PD7 Exhibit 1

Declaration of Professor Meredith Rosenthal
in Opposition to Defendants' Motion to Exclude My Opinions and Proposed Testimony

JULY 31, 2019

Contents

I. Overview

1. My name is Meredith B. Rosenthal. I was retained by the plaintiffs and filed an expert report on March 25 ,2019.[1] This declaration is filed in opposition to the defendants' Motion to Exclude Meredith Rosenthal's Opinion and Proposed Testimony, filed June 28, 2019.[2] This report is limited to addressing the larger, material issues raised in that motion and, to the extent that it relies upon the defendants' expert testimony, I address that testimony as well. I do not address remaining errors, misstatements and mischaracterizations made by the defendants' experts, although I reserve the right to do so if called to testify at trial. (I have been advised that there is no current procedural requirement to file a rebuttal report to the defendants' expert reports. If such a requirement is presented, I will prepare and file such a report).

2. Most fundamentally, the motion to exclude my testimony is predicated on a fundamental misunderstanding (or distortion) of the context and the allegations I was asked to assume the plaintiffs will prove at trial to the Court or the jury. Two aspects of this context are critical to an understanding of the way I approached my assignment and how a healthcare economist would address that assignment. First, the alleged misconduct was a market-wide phenomenon and included many different channels of influence, not all of which can be separately and precisely measured, but were deliberately mobilized to support the scheme to increase opioid sales.[3] Second, opioids are addictive goods and their chronic use leads to tolerance, often resulting in dose escalation.[4] Ignoring these facts leads the defendants to conclusions that are meaningless or simply wrong.

3. The motion also identifies what the defendants claim are methodological flaws in my analysis, including the failure to correct for endogeneity and unit roots. In so doing, they distort my report and

[1] Expert Report of Meredith Rosenthal, Ph.D., *In re National Prescription Opiate Litigation*, 290 F. Supp. 3d 1375 (J.P.M.L. 2017), March 25, 2019 (hereafter, "Rosenthal Report").

[2] Memorandum in Support of Defendants' Motion to Exclude Meredith Rosenthal's Opinions and Proposed Testimony, in this matter, June 28, 2019 (hereafter, "motion" or "Motion to Exclude").

[3] Second Amended Complaint Demand for Jury Trial, *In Re National Prescription Opiate Litigation*, United States District Court, For the Northern District of Ohio, Eastern Division, 17-MD-2804, (hereafter, the "Plaintiff Complaint"). Market-wide channels of influence include the use of front groups (*Ibid.* pp. 97-113), key opinion leaders (*Ibid.* pp. 113-124), medical education programs (*Ibid.* pp. 125-128), and unbranded promotion that targeted chronic pain and vulnerable patients (*Ibid.* p. 129 and pp. 136-138).

[4] J. Ballantyne and J. Mao, "Opioid Therapy for Chronic Pain," *The New England Journal of Medicine,* 349(20), 2003, pp. 1943-1953, p. 1945; D. Dowell, T. Haegerich, and R. Chou, "CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016," *Morbidity and Mortality Weekly Report*, 65(1), 2016, pp. 1-49.

my previous testimony. I demonstrate below that these criticisms are incorrect and the experts that offer them are in error.

4. At various points in the motion the defendants make legal arguments as to why my testimony should be excluded. Naturally, I do not have the expertise to address these legal arguments; however, if relevant I clarify points of incorrect healthcare economics or of incorrect facts that they appear to rely upon in those sections of their motion.

5. For all the experts the defendants have put forward to contradict my analysis, there is remarkably little of substance in the motion. Instead, the defendants primarily offer broad theoretical critiques without empirical validation (e.g., endogeneity, omitted variables), they cherry pick results (e.g., Dr. Kyle's placebo tests) to raise doubts about the meaning of my estimates, and they apply standard methods incorrectly. In summary, I show that the criticisms on which the motion rests do not stand up to scientific scrutiny and do not invalidate my earlier opinions.

6. The remainder of my report is organized as follows. In Section II, I address the defendants' opening claim that my analysis does not fit my assignment. Section III responds to the defendants' criticism of my measurement and modeling of promotional efforts, explaining how analyses accurately capture the impact of the alleged misconduct. Section IV examines and dismisses the remaining methodological issues related to my direct analysis that are highlighted in the motion. Section V and Section VI shows that the criticisms of my direct and indirect approaches are misguided, respectively. My summary and conclusion are contained in Section VII.

II. Motion to Exclude Incorrectly Asserts My Opinions Do Not Fit My Assignment

7. The defendants begin their motion by asserting that my analysis does not "tie to Plaintiffs' theory of the case."[5] In particular, they claim that by conducting a time-series analysis of all detailing on all opioid sales, I have somehow failed to fulfill my assignment. Because the question of "fit" supersedes all other technical criticisms the defendants attempt to use to undermine the empirical basis of my opinions, I address this issue first. In doing so, I review and reinforce the logical connections between my assignment and my analysis that I made repeatedly in my declaration and deposition. I also make clear that the analysis fits the nature of the public health crisis at hand – the opioid epidemic.

8. As noted in my original declaration[6], my assignment was four-pronged. In summary, I was asked:

[5] Motion to Exclude, p. 1.

[6] Rosenthal Report, ¶8.

1. whether the combined effect of the defendant manufacturers' promotion substantially contributed to the use of prescription opioids;
2. whether the increase in the use of prescription opioids in the Bellwether communities since 1995 would have occurred were it not for, i.e., "but for," the allegedly unlawful promotion of these products by the defendant manufacturers;
3. to quantify the increase in the use of prescription opioids in the Bellwether communities that resulted from the defendant manufacturers' allegedly unlawful promotion of prescription opioids since 1995; and
4. to quantify the sensitivity of the estimate of the impact of allegedly unlawful promotion on sales to the exclusion of individual defendants.

A. Time-Series Analysis Fits the Allegations

9. Time series analysis is designed to identify time-varying factors associated with the pattern over time of a data series that is measured at regular intervals. This is precisely the kind of problem my assignment presents – characterizing and quantifying the relationship between monthly changes in the stock of promotion and sales over time. Notably, many of the defendants' "omitted variables" critiques of my analysis have nothing to do with the correct time-series framing of the problem – they relate to patient- and physician-level factors that vary cross-sectionally but vary little over time or change in a way that suggests opioid use should have been declining, not growing. Thus, while these cross-sectional relationships might be of academic interest or relevant to some other question, they do not bring the Court or the jury closer to understanding the impact of the alleged misconduct on the sales of opioids over time.

B. An Aggregate Analysis Follows from the Allegations

10. My assignment, like the allegations in this matter, relates to the collective impact of conduct on the part of multiple manufacturer defendants over a period of more than 20 years. If the allegations are true, the manufacturer defendants both contributed to a widespread and deep change in the perception of the safety and efficacy of opioids *and* took advantage of this change as they reaped the increased profits that ensued. In the mid- to late 1990s, opioids went from being a treatment that was sparingly used in the United States to one that was widely and, at times, indiscriminately used.[7] One force behind

[7] A. Alam and D. Juurlink, "The prescription opioid epidemic: an overview for anesthesiologists," *Canadian Anesthesiologists' Society*, 63, 2016, pp. 61-68; M. Jones *et al.,* "A Brief History of the Opioid Epidemic and Strategies for Pain Medicine," *Pain and Therapy,* 7(1), 2018, pp. 13-21; and L. Manchikanti et al., "Opioid Epidemic

this change was the spotlight on pain management that pain guidelines and recommendations from organizations like the APS, AAPM, and TJC (formally JCAHO).[8] These guidelines were agnostic to the brand name of the product; they focused on case-finding and opioid treatment as a whole, not a particular opioid product. Thus, the development and dissemination of such guidelines are properly considered to be market-wide phenomena.

11. Clinical experts (like Dr. Schumacher and others) also attribute the change in opioid use to the defendants' efforts to break down previously-held beliefs about the risks from addiction alongside new and largely evidence-free efficacy claims for a wide range of chronic pain syndromes.[9] The common mechanism of action among opioids, and the apparent substitutability across molecules (see, for example, CDC treatment guidelines),[10] suggests that messaging to encourage physicians to see one opioid as safe and effective would likely have had positive spillover effects on other products. An analysis that myopically focuses on the impact of promotion within individual drugs only (such as that undertaken by the defendants' expert Professor Cockburn) would be incapable of capturing the effect of promotion on the sales of many opioids, a phenomenon known as "spillover effects." In other words, looking at the impact of marketing for one drug fails utterly to address the ability of the marketing fraud here to impact sales across the spectrum of prescription opioids—which is exactly the nature of the allegations here. Given that the ultimate goal of my analysis is to quantify the increased use of prescription opioids overall due to the misconduct, basic applied economics requires a method (like the one I used) that would ignore changes in market share alone. That is, if promotion was effective but only converted sales from Drug A to Drug B with no change in milligrams of morphine equivalent (MMEs), my approach should count that as zero impact.[11] Aggregating sales to the class-level inherently addresses

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in the United States," *Pain Physician,* 15(3 Suppl), 2012, ES9-ES38.

[8] I understand from counsel that the plaintiffs intend to prove that these guidelines were improperly manipulated by the defendants in the service of increasing sales despite the risks to population health. I return to these efforts later because the defendants' experts improperly identify these phenomena as "omitted variables" in my analysis, while they are in fact mediators that are explicitly called out in my analysis.

[9] Expert Report of Mark A. Schumacher, M.D., Ph.D., in this matter, March 25, 2019, Sections IV.A and IV.B.

[10] Centers for Disease Control and Prevention (CDC), "Clinical Evidence Review for the CDC Guideline for Prescribing Opioids for Chronic Pain – United States," 2016, pp. 1-25.

[11] In their brief, the defendants note that I do not attempt to exclude "rivalrous" marketing messages, Motion to Exclude p. 7. To the extent such messages have only rivalrous effects – shifts in market share – they have no effect on my outcome of interest. Research has found, however, that marketing cannot easily be classified in that way because rivalrous campaigns can have positive spillover effects on other brands, whether intended or not. See E. Berndt et al., "The roles of marketing, product quality, and price competition in the growth and composition of the U.S. antiulcer drug industry," *The Economics of New Goods*, University of Chicago Press, 1996, pp. 277-328, p. 278. For further evidence of the market-wide spillover effects of pharmaceutical promotion, see B. Shapiro, "Positive

this concern. For all of these reasons, an aggregate, class-level model was the appropriate methodology for my analysis.

C. The Nature of the Opioid Epidemic Informs the Analysis

12. Public health officials have been using the term "epidemic" to describe the opioid crisis for many years.[12] This language should be the first clue that any analysis of promotional effectiveness will yield different results than a study of the effect of promotion on the use, for example, of antacids. By definition, an epidemic is widespread; indeed, opioid addiction and overdose deaths have increased across all regions of the country, among rich and poor, educated and uneducated, and in virtually all racial and ethnic groups.[13] The term epidemic also connotes the infectious nature of utilization, addiction, and harm.

13. For the purposes of my analysis, the infectious nature of promotion is another reason to favor an aggregate analysis rather than focusing narrowly on the impact of detailing to an individual physician (as the defendants' expert Professor Cockburn does). An individual physician need not be directly detailed for her prescribing behavior to be influenced by promotion – for example, she may be influenced by senior physicians in her practice who were detailed.[14] Because a physician-level analysis

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Spillovers and Free Riding in Advertising of Prescription Pharmaceuticals: The Case of Antidepressants," *Journal of Political Economy*, 126(1), 2018, pp. 381-437; M. Rosenthal et al., "Demand Effects of Recent Changes in Prescription Drug Promotion," *Frontiers in Health Policy Research*, *Vol. 6*, MIT Press, 2003, pp. 1-26; and M. Sinkinson and A. Starc, "Ask Your Doctor? Direct-to-Consumer Advertising of Pharmaceuticals," National Bureau of Economic Research Working Paper No. 21045, 2015.

[12] Centers for Disease Control and Prevention (CDC), "Vital signs: overdoses of prescription opioid pain relievers−United States, 1999-2008," *Journal of the American Medical Association*, 306(22), 2011, pp. 2444-2446; J. Mendelson et al., "Addiction to prescription opioids: characteristics of the emerging epidemic and treatment with buprenorphine," *Experimental and Clinical Psychopharmacology*, *16*(5), 2008, pp. 435-441; L. Manchikanti et al., *op. cit.* ; and L. Paulozzi and G. Ryan, "Opioid analgesics and rates of fatal drug poisoning in the United States," *American Journal of Preventive Medicine*, 31(6), 2006, pp. 506-511.

[13] R. Rudd et al., "Increases in Drug and Opioid-Involved Overdose and Deaths – United States, 2010-2015," *Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report,* 65(50-51), 2016, pp. 1445-1442; A. Vivolo-Kantor et al. "Vital Signs: Trends in Emergency Department Visits for Suspected Opioid Overdoses – United States, July 2016-September 2017," *Centers for Disease Control and Prevention, Morbidity and Mortality Weekly Report,* 67(9), 2018, pp. 279-285; M. Cerdá et al., "Prescription opioid poisoning across urban and rural areas: identifying vulnerable groups and geographic areas," *Addiction*, 112, 2016, pp. 103-112; M. Alexander, M. Kiang, and M. Barbieri, "Trends in Black and White opioid mortality in the United States, 1979–2015.," *Epidemiology*, *29*(5), 2018, pp. 707-715; National Academies of Science, Engineering and Medicine, "Trends in Opioid Use, Harms, and Treatment," *Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use*, National Academies Press, 2017, pp. 187-265.

[14] For further discussion of the promotional ecosystem influencing physicians see Rosenthal Report, Section VI.C and Figure 1.

fails to measure all the indirect ways that promotion influences physicians (e.g., through peers, professional meetings), it will be biased towards a null result.

14. Finally, my analysis and its findings were influenced by the phenomenon at the heart of this litigation: addiction. It is now widely understood that opioids are inherently addictive[15], which means that once patients are exposed to them, some will continue consuming them for months or even years.[16] And because opioid use leads to tolerance, many patients will consume increasing daily doses (in MMEs) over time.[17] Such factual patterns suggest that promotion will have even more persistent effects than have been observed for other drugs and attributed to status quo bias on the part of physicians and patients (i.e., a reluctance to switch given uncertainty about alternatives).

15. For this and other reasons, I selected a standard analytic model that incorporates the stock of promotion with an empirically estimated depreciation rate. Rather than assuming a specific depreciation rate, this model allows *the data* to determine how long promotional effects last. My finding of a negative depreciation rate using this method – an *ap*preciation rate – is entirely consistent with the facts of chronic use leading to tolerance and addiction. The first prescription leads not only to a second prescription (and so on), but also to an escalating dose: the "asset" that a new patient represents to a pharmaceutical company continues to appreciate.

16. The defendants' criticisms of this empirical result are baseless (as I discuss further below). Not only do they turn a blind eye to the public health reality of the case at hand, but they nonsensically appear to suggest that it is somehow incorrect to observe that widely marketing an addictive product nationwide can lead to its use spiraling out of control.

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[15] I understand that at times, various of the defendants attempted to convince physicians that addiction would only occur in a subgroup of patients with addictive tendencies. For examples: Purdue messaged that "Copious evidence that the proper use of opioid medication for pain relief does not make patients vulnerable to addiction," PKY180425172-624, at 181; "The fact is, no one today has to suffer in pain, because effective medications, like opioids, are available and patients rarely become addicted or tolerant to opioids," PPLPC009000006347-351, at 348; and "Tolerance & physical dependence with opioid analgesics are not indicative of addiction...Addiction is a purely psychological disorder...Opioid tolerance is good…Odds of addiction in non-addicts from lawfully prescribed medications is 1/800 to <1/10,000" PKY180775599-707, at 648 and 650.

[16] B. Martin et al., "Long-term chronic opioid therapy discontinuation rates from the TROUP study," *Journal of General Internal Medicine*, 26(12), 2011, pp. 1450-1457.

[17] "Opioid tolerance is a pharmacologic phenomenon that develops with the repeated use of opioids and brings about the need to increase the dose to maintain equipotent analgesic effects; it reduces the efficacy of opioids and may be a reason for dose escalation." Ballantyne and Mao, *op. cit.*

III. Motion to Exclude Incorrectly Claims that I Do Not Measure the Effect of Defendants' Allegedly Unlawful Conduct

17. The defendants claim that my model fails to measure the effect of the defendants' *unlawful conduct* on sales.[18] This erroneous conclusion derives from a failure to distinguish two elements of my direct analysis.

18. First, I investigate the extent to which promotion affects sales of opioids in MMEs. This is done using a national, aggregate model while accounting for prices and other factors such as unbranded marketing effects and countervailing public health efforts. In doing so, I apply an empirical model that quantifies the extent to which promotion affects sales of pharmaceuticals. My methodology has been used in peer-reviewed, academic literature[19] and previously accepted by the Federal Court.[20] This portion of the empirical work does not distinguish between defendant and non-defendant, or between fraudulent promotional messages versus lawful messages.

19. Second, my investigation uses the estimated relationship between promotion and sales to determine how much sales would change if the level of promotion changed. This is the step where the notion of "harm" is introduced and (contrary to the assertions in the motion) it is here that I estimate the "harm resulting from Defendants' *un*lawful conduct."[21] My model is agnostic about whether promotion is lawful or unlawful. It is when *applying* the results of my model to estimate MMEs in the "but-for" world that I provisionally make the assumption that "the fact finder … finds that all or virtually all promotion by the manufacturer Defendants from 1995 to the present was unlawful."[22] As I state in my report, "I later show that the model I present can be adjusted to reflect other assumptions about the fact finder's conclusions,"[23] ensuring that the methodology is robust enough to be useful in a panoply of scenarios.

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[18] Motion to Exclude, pp. 5-6.

[19] E. Berndt et al., "Information, Marketing and Pricing in the U.S. Antiulcer Drug Market," *American Economic Review*, 85(2), 1995, pp. 100-105. J. Rizzo, "Advertising and Competition in the Ethical Pharmaceutical Industry: The Case of Antihypertensive Drugs," *Journal of Law and Economics*, 42(1), 1999, pp. 89-116. Defense expert, Dr. Kyle co-authors a report that uses a similar model: D. Ling, E. Berndt, and M. Kyle, "Deregulating Direct-to-Consumer Marketing of Prescription Drugs," *The Journal of Law and Economics, 45*(S2), 2002, pp. 691-723.

[20] *In Re Neurontin Marketing and Sales Practices Litigation*, MDL NO. 1629. Civil Action No. 04-cv-10981-PBS (hereafter, "Neurontin MDL (Kaiser)").

[21] Motion to Exclude, p. 1. (emphasis in the original)

[22] Rosenthal Report, ¶ 75.

[23] *Ibid.*

20. The motion also appears to take issue with the fact that I do not attempt to prove the unlawful nature of the conduct whose impact I have been asked to ascertain.[24] But this is clearly absurd given my assignment and expertise. I do, however, demonstrate that I have examined the reasonableness of the assumptions that I was given by counsel. In Section VII of my affirmative report, I identify examples of misleading promotion including that deemed unlawful in court (e.g., Purdue pled guilty to various forms of unlawful conduct in 2007[25], former Insys CEO pled guilty to conspiracy and fraud[26]).

A. The Motion Incorrectly Asserts My Analysis Fails to Account For Front Groups, Key Opinion Leaders, and Continuing Medical Education.

21. Contrary to the assertions in the motion, I do take account of the defendants' efforts to leverage third-party groups and key opinion leaders (KOLs). I also take account of the influence of countervailing public efforts to stem the tide of opioid prescriptions, addiction and harm from opioid overdoses. In a sensitivity analysis, I include the variables for key third-party efforts directly in the model. In my preferred model, I incorporate these efforts by recognizing that they collectively conditioned the environment in which promotional messages were being transmitted, leading to changes in the effectiveness of promotion over time. Because of the number and timing (i.e., some efforts might have an immediate effect, while others diffused more slowly) of non-traditional promotional efforts (and later, public health counter-measures), simply including them in a model as "events" would lead to not reliably capturing their true effects. Indeed, when I include a subset of event variables in a sensitivity analysis, most are statistically insignificant, and one has a counterintuitive sign. Instead, I captured the net effects of the non-traditional (and largely unbranded) marketing and countervailing public efforts using a model that allowed promotional effectiveness to vary over time, a standard approach in the economics literature.[27] In particular, I used empirical methods to identify an *acceleration* in promotional effectiveness because the defendants' efforts to relax previous norms of opioid use proliferated and a *deceleration* in promotional effectiveness when public health counter-measures gained ground.

[24] Motion to Exclude, pp. 5, 10-11.

[25] Rosenthal Report, ¶ 47, referencing *US v. Purdue Frederick Co., Inc.*, 495 F. Supp. 2d 569 (W.D. Va. 2007).

[26] *Ibid.,* referencing *U.S. v. Kapoor*, 16-cr-10343, U.S. District Court, District of Massachusetts.

[27] See, for example, a paper cited by defendants' expert Garthwaite on opioid deaths and the reformulation of Oxycontin: W. Evans, E. Lieber, and P. Power, "How the reformulation of OxyContin ignited the heroin epidemic," *the Review of Economics and Statistics,* 101(1), 2019, pp.1-15. The paper uses a similar methodology for estimating an inflection point in the data.

Moreover (and as noted in my affirmative report[28]) to the extent that the defendants deployed physician-directed marketing tactics such as speaker dinners with key opinion leaders and other forms of peer-to-peer marketing, the pharmaceutical marketing literature suggests they are complements to detailing and thus will rise and fall together.[29] In that case, my analysis picks up the combined effect of these efforts. Thus, my *direct* analysis indeed accounts for the use of front groups, key opinion leaders and other promotional tactics. And my *indirect* analysis is designed precisely to capture promotional efforts influencing sales growth beyond detailing, which is the most reliably measured form of promotion.

B. The Motion to Exclude Falsely Claims that I Make "Baseless Assumptions"[30] To Ensure My Conclusions

22. The motion asserts that my estimates of the effects of opioid promotion on sales come from a model that is "contorted and 'overfit'" to "ensure" my conclusions.[31] Supposedly I "manipulated"[32] my estimates of delayed effects of promotion on sales and of shifts in opioid prescribing over the 1993-2018 period, to get the result that "99 percent of opioid prescriptions were dispensed solely on the basis of manufacturer detailing."[33]

23. This is a gross misrepresentation of both my findings and my model. The claim that my model shows detailing alone to explain 99 percent of MME sales is simply false. The model explains changes in the level of opioid sales over time as a function of changes in opioid detailing, opioid prices, and policies and attitudes towards opioid prescribing. The explanatory variables taken together explain 99% of the *variation* in MME sales -- not 99% of sales. The explanatory power comes from the full set of explanatory variables in the regression, not manufacturer detailing alone. As such the Motion's claims are either based on an incorrect understanding of econometric analysis or are intentionally false and misleading.

[28] Rosenthal Report, ¶ 56.

[29] H. Nair, P. Manchanda, and T. Bhatia, "Asymmetric social interactions in physician prescription behavior: The role of opinion leaders," *Journal of Marketing Research*, *47*(5), 2010, pp. 883-895.

[30] Motion to Exclude, op. 11.

[31] *Ibid*.

[32] *Ibid*., p. 12.

[33] *Ibid*., p. 11.

24. Moreover, far from making "baseless assumptions" to get the model to produce desired results, my model appropriately *estimates* key parameters, to avoid the possibility that arbitrary assumptions could sway the results. The motion claims that this results in a regression model that "contains so much flexibility" that it can also find "a causal relationship between physician detailing on the one hand and sunspots, gold prices, or baseball attendance on the other."[34] As I discuss below, this claim is based on defendants' experts cherry-picking "placebo tests" in which their implementations of my model yield implausible results; as I show, small changes in specification, like shifting the data period, substantially affect these results. Rather than being unusually flexible, my model is solidly in the mainstream of preferred practice in applied econometrics, which *estimates parameter values* from the data rather than imposing them in advance.

C. The Motion Incorrectly Implies that My Assignment Included Computing Harm Arising from Individual Defendants.

25. I was not asked to examine separately the impact of each individual defendant's conduct. Moreover, as I noted earlier, a single-manufacturer analysis would not properly capture the outcome of interest – the overall level of opioid use in MMEs. The estimated effectiveness of promotion on sales for an individual manufacturer may misstate the impact on the market as a whole because some or all of a firm's sales growth may occur at the expense of sales by another firm, thus resulting in a lower (or no) impact on national sales.

26. My analysis does allow the Court to examine the incremental impact of any manufacturer's promotion efforts on market-wide sales, as shown in Table 3 of my affirmative report.[35] Should the Court find that proof of unlawful conduct is lacking for any particular manufacturer defendant for any time period, the associated promotional efforts can be considered lawful in a but-for scenario. Thus, my methodology is capable of treating the defendants individually, albeit in an aggregate analysis that properly captures the interactions between their efforts.

D. The Motion Misrepresents My Treatment of Lawful and Unlawful Detailing.

27. The motion criticizes me for failing to distinguish between fraudulent and lawful promotion.[36] When I estimate the impact of detailing, I implicitly make the assumption that the effectiveness of a

[34] *Ibid*., p. 12.

[35] Rosenthal Report, Table 3.

[36] Motion to Exclude, pp. 6-7, 10-11.

fraudulent detailing visit is the same as the effectiveness of a lawful detailing visit. This is a conservative assumption and it is one for which there is support in the academic, peer-reviewed literature. Empirical studies of unlawful conduct are naturally rare, due to the difficulty of obtaining data. One published paper that does explicitly address the effect of fraudulent detailing messages was able to obtain call notes produced by Pfizer in a Neurontin case that went to trial. The paper found that the effectiveness of fraudulent messages was not statistically different from that of detailing messages that did not contain fraudulent messages.[37] The authors found statistically similar impacts of approved messages and unapproved messages on physicians' intentions to prescribe.[38]

28. Using elementary economic analysis, one must conclude that the return to illegal behavior is greater than the return to legal behavior; otherwise it would not be rational to engage in the illegal behavior. The economic theory of crime is a well-developed body of economic literature and research. The expected return to illegal behavior must be higher than lawful behavior so as to compensate for the risk of potential penalties if caught.[39]

IV. Responses to Individual Methodological Critiques

29. In this section, I address the more detailed methodological critiques suggested by the defendants' experts and relied upon in the motion. While I elude to these issues above, in this section, I offer more granular arguments and data analysis to show that their critiques are baseless and ill informed.

A. The Negative Depreciation Rate is Empirically and Theoretically Valid

30. In the motion, the defendants argue, "Rosenthal estimated a *negative* depreciation rate for promotion…. Not only is such a theory of the forever-ascending potency of marketing illogical, but

[37] M. Steinman et al., "Characteristics and impact of drug detailing for gabapentin," PLoS Medicine, 4(4), 2007, pp. 743-751. See also, Rosenthal Report, ¶ 35

[38] *Ibid.,* p. 743. In drawing inferences from this finding, the authors conclude "physicians reported similar increases in future prescribing or recommending of gabapentin after exposure to approved or unapproved messages," *Ibid.,* p. 747.

[39] Becker finds that firms will engage in fraudulent or criminal activity when profits are greater than cost of penalties such as fines and legal fees, leading him to highlight "'[t]he evil of the punishment must be made to exceed the advantage of the offense' (Bentham, 1931, first rule)," G. Becker, "Crime and Punishment: An Economic Approach," *University of Chicago Press,* 1968, pp. 169-217, p. 191. Similarly, Becker and Murphy show that illegal drug distributors adjust their behavior, such that the expected profits outweigh the costs incurred with the risk of being caught. G. Becker and K. Murphy, "The Market for Illegal Goods: The Case of Drugs," *Journal of Political Economy*, 114(1), 2006, pp. 38-60.

Rosenthal expressly recognized that no economic literature supports it."[40] The defendants' critique of my findings rests largely on (i) the absence of a published precedent and (ii) an ignorance of the fundamental facts of the public health context of this matter.

31. There is nothing illogical about the negative depreciation rate that I estimated—it is an empirical fact derived from acceptable data, well-known and accepted econometric techniques, and fits something the defendants' attacks lack, common sense. The estimated depreciation rate uses a standard methodology that has been used in other studies of pharmaceutical promotion. My results can be explained by the facts of this case and a close examination of the underlying data. While it is true as I said in my deposition that I am not aware of any marketing studies that have found a negative depreciation rate for the stock of promotion, the reason for this is simple—no studies (at least that I am aware of and the defendants have not cited any) have attempted to estimate a depreciation rate for promotion in a similar, addictive product context.

32. In this section, I begin by showing an empirically-based illustration of how a negative depreciation rate matches the nature of opioid addiction. This illustration also demonstrates how the unit of analysis (MMEs vs. prescriptions) in my model affects the depreciation rate that I estimate, explaining at least part of the difference between what I find and depreciation rates estimated in the pharmaceutical literature. Finally, I show by careful examination of the literature on the effects of promotion for pharmaceuticals as well as for tobacco and alcohol (as proposed by the defendants' experts) that there is no contradiction between the published literature and my estimates.

33. I selected a standard analytic model that incorporates the stock of promotion with an empirically optimized depreciation rate. Rather than assuming a specific depreciation rate, this model allows *the data* to determine how long promotional effects last. The defendants' brief does not criticize the conceptual use of a stock of promotion as an explanatory variable. In fact, the defendants' expert Dr. Kyle was a co-author on a paper that used a similar model of the stock of promotion.[41] This empirical model has been used by economists in multiple and widely cited peer-reviewed papers,[42] in previous litigation,[43] and has been recognized by the Court during the course of a trial.[44] With a few

[40] Motion to Exclude, p. 11.

[41] D. Ling, E. Berndt, and M. Kyle, *op. cit*.

[42] *Ibid*.; Berndt et al., 1995, *op. cit*.; and Rizzo, *op. cit*.

[43] Neurontin MDL (Kaiser).

[44] Expert Report of Meredith Rosenthal, Ph.D., in the matter of Neurontin MDL (Kaiser), August 11, 2008, (hereafter, "Rosenthal Neurontin MDL Report"). This report is publicly available at:

exceptions, which I address below, none of the opposing experts provided an alternative model that addressed either the long-lasting effects of promotional advertising on sales, nor the implications of addressing the sales patterns of an addictive drug.

1) My Estimates Capture Widely Understood Phenomena in this Market

34. The defendants' experts' critique of the negative depreciation rate can be dismissed with a basic examination of the facts in the opioid context. The notion that a single detailing visit could have an increasing impact over time is not at all unreasonable. Any one of the following phenomena (or any combination thereof) could lead to such a pattern: (1) increasing tolerance leading to higher dosages per patient; (2) physicians lowering the threshold for opioid prescribing over time (for example, expanding use from acute pain patients to chronic pain patients); and (3) changes in local or institutional norms that lower the barriers to opioid prescribing (e.g., hospital administrators encourage greater use of opioids in response to new JCAHO guidelines for pain management).

35. One of the defendants' experts, Dr. Grabowski, purports to show the unreasonable nature of a negative depreciation rate using the underlying data on MME sales.[45] A more careful look at all the data, however, shows that accounting for only the first of the phenomena listed above (increasing MMEs per prescription) makes the findings of my analysis comparable to published depreciation rates for other pharmaceuticals. To see this, I begin by presenting the number of MMEs per prescription over time as shown in Figure 3 of my affirmative report, replicated below in Figure 1.

36. Figure 1 shows that in 1995 there were, on average, approximately 350 MMEs per prescription. By 2010 opioid dosing had risen by more than three times to approximately 1,100 MMEs per prescription. Since guidelines suggest that "naïve" patients taking opioids be started on low doses, this pattern may be the result of the increase in chronic use of opioids, whereby patients develop tolerance to opioids and thus require higher doses to combat their pain.[46] Alternatively, physicians may have

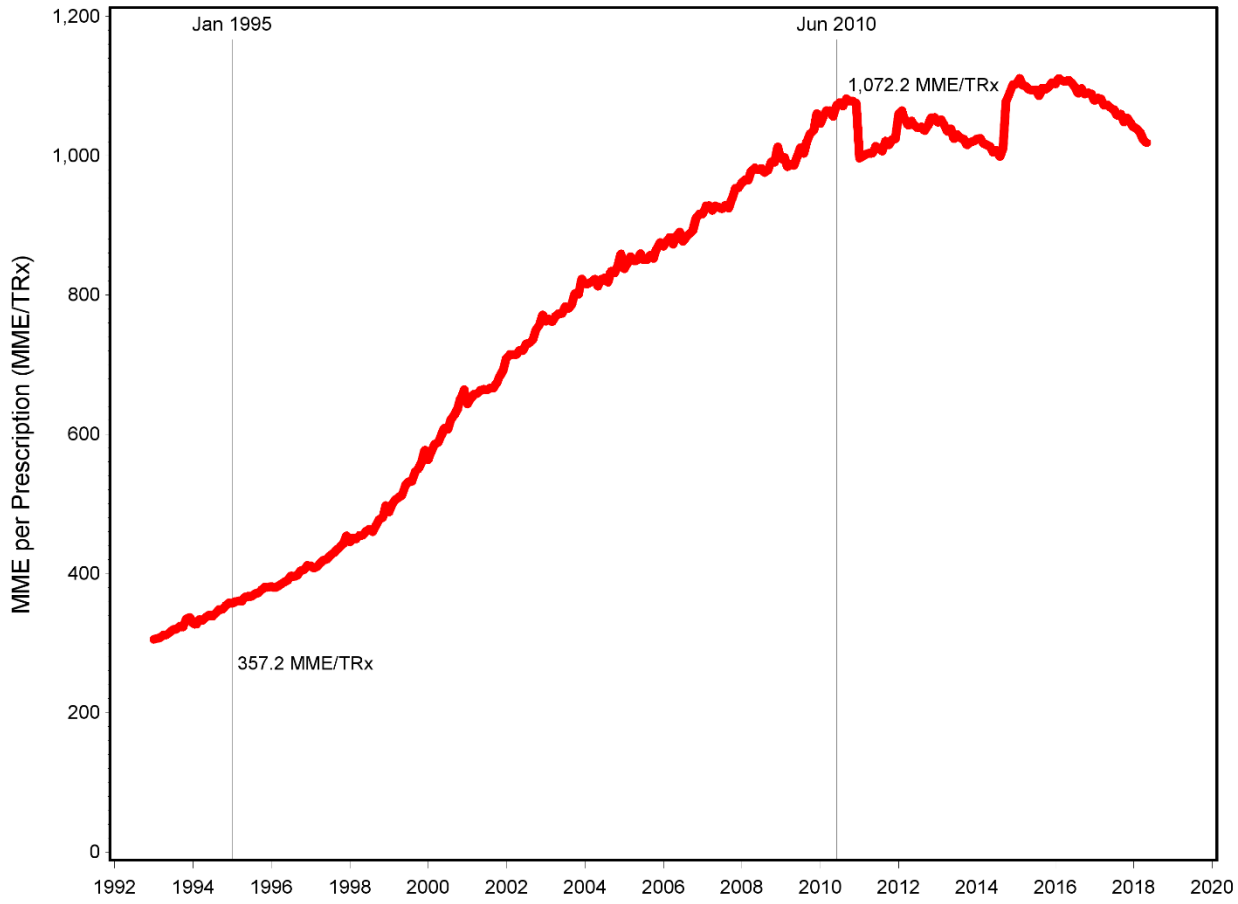
https://www.communitycatalyst.org/pal-docs/neurontin_exh_F.pdf

[45] Expert Report of Henry Grabowski, Ph.D., in this matter, May 10, 2019 (hereafter, "Grabowski Report"), ¶¶75-78.

[46] "Opioid tolerance is a pharmacologic phenomenon that develops with the repeated use of opioids and brings about the need to increase the dose to maintain equipotent analgesic effects; it reduces the efficacy of opioids and may be a reason for dose escalation." J. Ballantyne and J. Mao, *opt. cit*.; Shands at The University of Florida, "Opioid Prescribing in "Naïve" or "Tolerant" Patients," *Drugs and Therapy Bulletin,* 26(3), 2012, pp. 1-4; and M. Barnett et al., "Opioid-prescribing patterns of emergency physicians and risk of long-term use," *New England Journal of Medicine*, 376(7), 2017, pp. 663-673.

increased starting doses of opioids over time in accordance with the decreased concerns about the potential for addiction.[47]

Figure 1. MMEs Per Prescription, All Opioids, 1995-2018

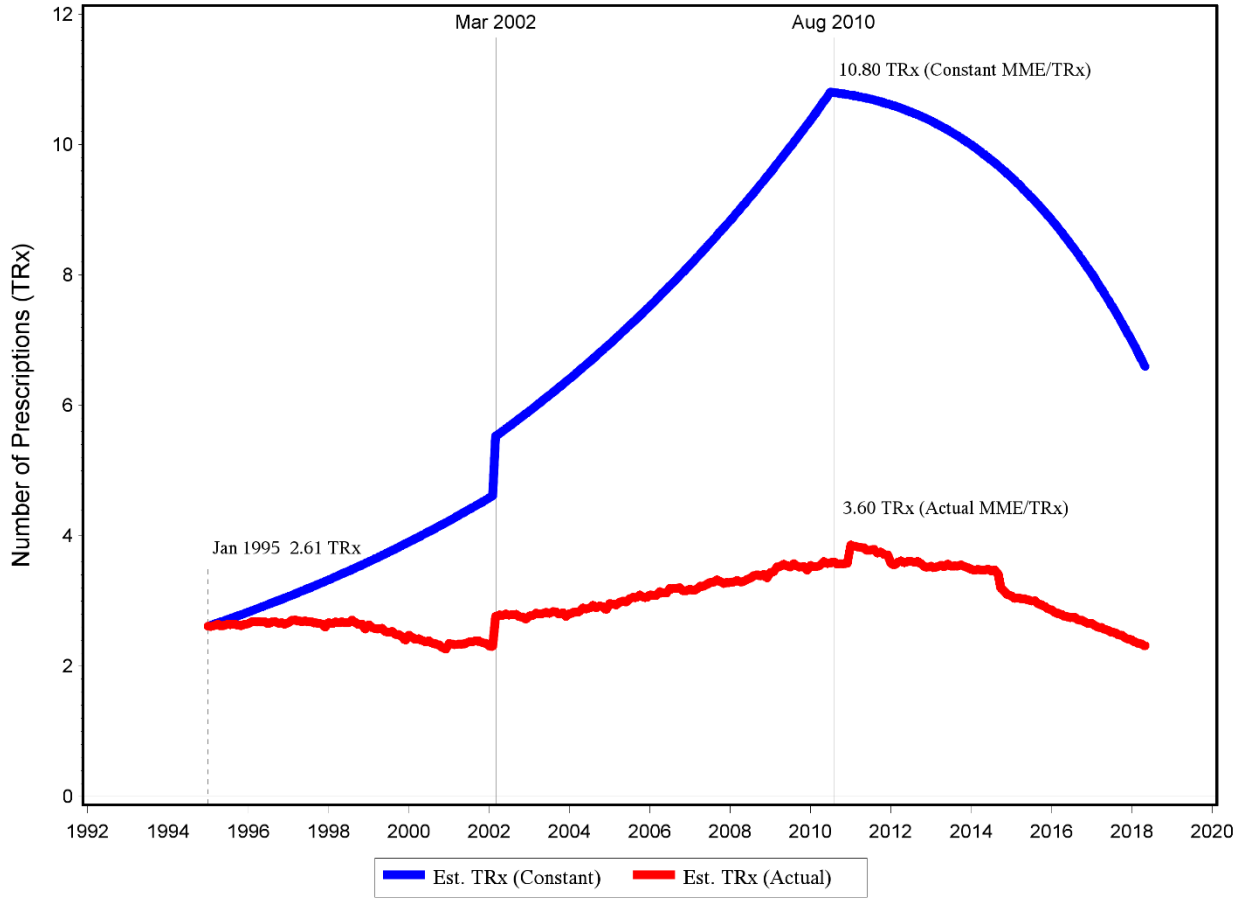


37. Dr. Grabowski's analysis shows that more MMEs are induced in a given period (January 2010) by a detail 15 years ago (in January 1995) than are induced by a detail in the same period (January 2010). This result is entirely consistent with naïve patients consuming lower doses of opioids than long-term users as well as changing norms of prescribing, which may affect current naïve patients differently than long-term users. However, Dr. Grabowski misses the fact that the increase in MMEs is not proportionate to the increase in the number of prescriptions, which was much less.

[47] D. Dowell, T. Haegerich, R. Chou, opt. cit.; A. Kolodny et al., "The prescription opioid and heroin crisis: a public health approach to an epidemic of addiction." Annual Review of Public Health, 36, 2015, pp. 559-574, p. 562; ACTAVIS0006823-830 at 826; PKY180425172-624 at 181; PPLP003516982-997 at 986.

38. Without controlling for the growing MMEs/TRx during this period, Dr. Grabowski's analysis predicts that in August 2010 the detailing event from January 1995 would cause about 10.81 prescriptions in that month, a 414% increase.[48] Dr. Grabowski points to this consequence as an "implausible implication."[49] However, if we control for the rising MMEs per prescription, we see that the 2.61 prescriptions from 1995 turned into about 3.60 prescriptions, a 38% increase in prescribing in 15 years, which could easily be the result of physicians who were initially caused to prescribe to one type of patient expanding the use of opioids to more of their patients over time.

Figure 2 Estimated Number of Prescriptions per Month from 1 Detail Visit



39. The defendants' documents also affirm that past detailing plays a significant role in current sales. In 2013, Purdue reported that 86% of OxyContin Prescriptions within a 6-month period are

[48] Accounting for the average MME per prescription (TRx) in January 1995, the starting point is 2.61 TRx. Without dividing the predicted MMEs by the January 1995 value of MME per TRx we get the values shown in Figure 2 by the blue line that peaks in August 2010 at 10.80 TRx.

[49] Grabowski Report, ¶ 75.

"Continuing Rx's" from previous periods while the remaining 14% are new prescriptions.[50] Endo documents similarly show that from January 2011 to December 2011 OPANA "carryover sales," or "sales that occur due to SF [Sales Force] promotion in previous years" drive the majority of sales (at 81.3% or $311 million or $383 total net sales).[51]

40. In summary, a number of plausible explanations exist for the growing impact of a detailing contact over time; increases in dosing for both new and chronic patients and "indication creep" where opioid prescribers lower the bar for using opioids over time, are two of the most obvious ones. My calculations show how just one of these, increases in dosing, could well account for the appreciation of the promotional stock over time.

2) Motion to Exclude Misrepresents Findings from the Economic Literature

41. In their attempt to discredit my finding of a negative depreciation rate, the defendants rely on the testimony of Dr. Grabowski: "Henry Grabowski also testified that he has never seen a negative depreciation rate, as consultants confirmed through a diligent literature search. (Ex. 7, Grabowski Dep. at 38:12–39:7.)."[52]

> "I said there is a -- a literature here on the effects of promotion. And particularly, you know, I -- I have done work in this area, so I know the literature well. But for instance, Dr. Rosenthal has found a negative depreciation rate, which I said I never have seen this in my professional experience. And she claims it's due to -- it can be explained by the fact that opioids are addictive, but there are other work on addictive substances, marketing of addictive substances, like cigarettes and alcohol, that has been undertaken, some by me and some by others. And I want you to see if I'm right, that there -- that you can find anything in the literature that has a negative depreciation rate. And in the context of that, they looked at stuff -- some more articles. They searched the literature diligently, but they could not find anything."[53]

42. The literature review is described in Dr. Grabowski's expert report, where he responds to my explanation that a negative depreciation rate is "perfectly consistent with an addictive product like opioids."[54] He states, "Dr. Rosenthal does not cite to any academic marketing literature to support this

[50] PPLPC030000784359 at slide 8.

[51] ENDO-CHI_LIT-00214471 at slides 37 and 62.

[52] Motion to Exclude, pp. 11–12.

[53] Declaration of Timothy W. Knapp in Support of Defendants' Motion to Exclude Meredith Rosenthal's Opinions and Proposed Testimony, June 28, 2019 (hereafter, "Exhibit to Motion to Exclude"), Exhibit 7, 38:12–39:7.

[54] Grabowski Report, ¶ 91.

point."[55] He claims to do his own review of the literature on marketing of addictive substances and concludes, "studies of the effect of marketing on rates of use of addictive substances, such as cigarettes and alcohol, find positive depreciation rates."[56]

43. Dr. Grabowski's statement is simply not supported by the literature, however. First, half of the articles Dr. Grabowski cited did not actually *estimate* a marketing depreciation rate. In Gruber and Köszegi, the authors conclude, "We [have not] been able to pin down *d* [the depreciation rate] empirically,"[57] and, "Physiological and empirical evidence suggests that λ^{*s} is fairly high for smoking. *Evidence is less clear on the depreciation rate*."[58] In Ross et al. (2015) and Siegel et al. (2016), both articles *assumed* a 50% [[monthly]] depreciation rate – but neither article computed this rate; instead, they imported it from a single study of consumer products advertising (i.e., non-addictive goods). Ross et al. stated, "The rate of advertising depreciation for *most consumer products* has been estimated; Broadbent reported a half-life of 3–4 weeks, or approximately one month (Broadbent, 1997)."[59] Siegel et al. stated, "The half-life of advertising for *most products* is approximately four weeks [also citing Broadbent 2007]. Thus, to estimate a brand's adstock value at the end of 2011, we summed December's GRPs with a depreciating proportion of prior months' GRPs, using a decay rate of 50% per month."[60]

44. While Dave and Saffler (2016) estimate a depreciation rate using actual data, their methodology biases their results upwards. To estimate the long-term effect of magazine advertising on smokeless tobacco users, this study depends on the subjects' recall of the magazines they read in the past six months, which is likely to be unreliable. Therefore, to the extent that the study finds a stronger impact of magazines read in the past month compared to six months ago, this is just as likely an effect of the subjects' poor recall of exactly what magazine they read six months ago.[61]

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[55] *Ibid.*

[56] *Ibid.*

[57] J. Gruber and B. Köszegi, "Is Addiction "Rational"? Theory and Evidence," *The Quarterly Journal of Economics*, November 2001, pp. 1261-1303, p. 1291, *emphasis added*.

[58] *Ibid*., *emphasis added*.

[59] C. Ross et al., "The Relationship Between Population-Level Exposure to Alcohol Advertising on Television and Brand-Specific Consumption Among Underage Youth in the US," *Alcohol and Alcoholism*, 50(3), 2015, pp. 358–364, p. 360.

[60] M. Siegel et al., "The Relationship Between Exposure to Brand-Specific Alcohol Advertising and Brand-Specific Consumption among Underage Drinkers—United States, 2011-2012," *The American Journal of Drug and Alcohol Abuse*, 42(1), 2015, pp. 1-11, p. 3.

[61] The study describes the data collection method: "For each magazine, the individual reports whether they read or looked into it in the past six months. Respondents further report on the number of issues that they read out of every four issues, on average. This information can be used to construct an individual-specific probability of

45. Second, none of these studies analyzed the effect of marketing to doctors or a comparable "agent;" they focus instead on marketing directly to consumers. Marketing to doctors has a stronger potential for long-term impact than marketing to consumers. Each doctor has many patients but does not see most patients every month. Therefore, if a doctor is convinced by a detailing visit that more chronic-pain patients should be treated with opioids, there is a potential that the number of that doctor's patients receiving opioid prescriptions could increase steadily over many months or even years because of the doctor's changed opinion. Furthermore, if a doctor begins prescribing more opioids and gains a reputation for a willingness to do so, then patients seeking opioids may switch to that doctor.[62] There is not the same potential for long-term sales growth from marketing to individual consumers.

46. Third, most of the studies estimate the effect of brand-specific marketing on the sales or market share of specific branded products. Ross et al. (2015),[63] Siegel et al. (2016),[64] Peles (1971),[65] and Schnabel (1972)[66] all fall into this category. The effect of advertising at the branded product level depreciates more rapidly than its effect at the industry or therapeutic class level, as found by Berndt et al. in their study of antiulcer drugs:

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reading an issue of each of the 198 magazines, ranging from 0 for those who did not read the magazine at all to 1 for those who read all issues of the magazine" D. Dave and H. Saffer, "Demand for smokeless tobacco: Role of advertising," *Journal of Health Economics,* 32(4), 2013, pp. 1-33, p. 12.

[62] D. Wilber, "12 million pills and 700 deaths: How a few pill mills helped fan the U.S. opioid inferno," *Los Angeles Times*, June 14, 2019 (https://www.latimes.com/nation/la-na-pol-pill-mills-linked-to-hundreds-of-deaths-20190614-story.html).

[63] "At the population level, underage youths' exposure to brand-specific advertising was a significant predictor of the consumption prevalence of that brand, independent of each brand's price and overall market share." Ross et al., *op. cit.,* p. 358.

[64] "Underage youth were more than five times more likely to consume brands that advertise on national television and 36% more likely to consume brands that advertise in national magazines" Siegel et al., *op. cit.,* p. 1.

[65] In Peles, the article makes firm-specific calculations of the amortization of advertising; thus it is not a market-wide analysis: "This article measures the effect of advertising expenditures on the firm's sales in three industries: beer, cigarettes, and new passenger cars" Y. Peles, "Rates of Amortization of Advertising Expenditures," *Journal of Political Economy*, 79(5), 1971, pp. 1032-1058, p. 1032.

[66] In Schnabel, the article applies the depreciation rate when computing the effect of individual brands' marketing on their market share: "[T]his fraction was allocated among the brands in proportion to their shares of good will. A unilateral increase in a brand's level of advertising would increase its share of good will and thus increase its share of advertising-oriented consumers; but, because shares of good will were based on shares (not levels) of advertising, the increase in its share of good will would decline as its starting level of advertising rose. The distributed lag form assumed for the weights in computing shares of good will meant that a brand's share of good will depreciated at the rate 1 - r; that is, if the brand did not advertise in the current period, its share of good will would be the portion r of what it had been last period" M. Schnabel, "An oligopoly model of the cigarette industry," *Southern Economic Journal*, 38(3), 1972, pp. 325-335, p. 328.

> "[A] somewhat unexpected result we obtained is that at the industry level, the rate of depreciation of stocks of both minutes of detailing and medical journal advertising was estimated to be zero. We believe that this result reflects the fact that market-expanding marketing primarily involves informing physicians about the usefulness of this class of drugs, and that once a physician begins prescribing these drugs, he or she is not likely to forget about their existence and stop prescribing them. By contrast, at the level of market shares a rather different picture emerges. In particular, in the four-product market (Tagamet, Zantac, Pepcid, and Axid), we find that the market-share impact of the stock of detailing minutes deteriorated at an annual rate of around 40 percent, reflecting perhaps a more rivalrous content of marketing efforts."[67]

47. Fourth, none of the studies analyze the market for prescription opioids; they focus on other addictive goods: cigarettes, alcohol, and smokeless tobacco products (chewing tobacco and snuff).[68] The markets and demands for these other products are significantly different from the market for prescription opioids where other factors affect demand, e.g., physician agency and health insurance. I would not expect the marketing depreciation rates to be the same.

48. Thus, none of the studies cited by Dr. Grabowski show what he and the defendants claim they show. The additional study referenced in the defendants' brief, Hirschey (1982), is also not relevant. It is a study of the effect of a firm's total advertising expenditures on the firm's total market value, and as part of that analysis it estimates the depreciation of the goodwill from those advertising expenditures.[69] This study does not consider marketing for addictive substances; it studies the effects of a firm's advertising on its *own* market value, not on a market-level analysis.

49. Finally, I would note that my estimated negative depreciation rate fits within with my own previous work and the literature on pharmaceutical promotion in general. In previous cases where I analyzed the impact of promotion on sales, I have estimated depreciation rates equal to zero. For example, in the Neurontin MDL case my assignment was different than in the current matter (notably it was a product-level analysis), but I did compute depreciation rates. I estimated eight models for four indications (Bipolar, Migraine, Neuropathic Pain, and Nociceptive Pain). For two of those indications' promotion was examined for three specialties. In four of eight models I obtained estimates of a zero

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[67] E. Berndt et al., 1996, *op. cit.,* pp. 311-312.

[68] ***Three of the articles study cigarettes*** (J. Gruber and B. Köszegi, *op. cit.*; Y. Peles, *op. cit.*; and M. Schnabel, *op. cit.)*; ***two study alcohol*** (C. Ross et al., *op. cit.*; and M. Siegel et al., *op. cit.*); and ***one studies smokeless tobacco*** (D. Dave and H. Saffer, *op. cit.*).

[69] Motion to Exclude, p. 12, Ex 8., M. Hirschey, "Intangible Capital Aspects of Advertising and R&D Expenditures," *The Journal of Industrial Economics*, 30(4), 1982, pp. 375-390.

depreciation rate.[70] This finding is replicated in peer-reviewed studies including one coauthored by the defendants' expert Dr. Kyle, as noted earlier. Given that my analysis here is *class-level* and focused on *detailing contacts* (as opposed to consumer advertising) I would expect to find relatively long-lived and even appreciating promotional effects.

50. In summary, the defendants cannot rely on the published literature to refute my estimated negative depreciation rate. The studies they claim offer contradictory evidence do no such thing, but instead corroborate my findings once the special nature of opioid prescribing is accounted for.

B. Placebo Tests

51. The motion incorporates the work of the defendants' experts who attempt to discredit my analysis by introducing so-called "placebo tests."[71] Placebo tests are intended to show that an estimated effect is specific to the context of interest. By design, placebo tests are counter-theoretical – they relate two data series that the analyst proposes should be unrelated. Notably, placebo tests can be used to raise but not answer causal questions – there is no universal theory that says if a significant effect is found on an unrelated outcome that the main estimate cannot be true.

52. Importantly, the defendant's experts have used the placebo test in a way not intended by cherry-picking their placebos. The most blatant and egregious example of cherry-picking comes from Dr. Kyle in her selection of sunspots that fall within a carefully selected window of 179 months running from January 1997 to November 2011. Dr. Kyle's selection of this window of time resulted in a R-squared of 88%. However, if all NASA data available on or after January 1993 were used the R-squared would fall to 55%, which apparently was not sufficiently compelling for Dr. Kyle's purposes. These results are shown in Appendix A.

53. Since there is no theorized causal relationship between sunspots and MME sales, there is no reason to assume that the month of the sunspots needs to correspond to the month of the MME sales to construct a placebo. Based on this premise, I have extended Dr. Kyle's so-called placebo test to 25 randomly selected windows of 305 months from her NASA data series of average monthly sunspots

[70] Rosenthal Neurontin MDL Report Attachment F: Table 2, Table 5, Table 6, and Table 7. The depreciation rate can be determined from the regression output and the three-digit label of the baseline promotion variable, e.g., LBOTHER_000 has a deprecated rate of 0%.

[71] See for example, "[I]f one were to replace MME sales in her model with data from NASA concerning the monthly average of daily sunspots, the price of gold, or the average yearly attendance at Cleveland Indian baseball games, one applying her model would find a causal relationship between physician detailing on the one hand and sunspots, gold prices, or baseball attendance on the other" Motion to Exclude, p. 12. (Kyle uses sunspots; Ketcham uses gold prices, McCrary uses average yearly attendance at Cleveland Indian baseball games).

which dates back to 1794. The distribution of R-squared values range from 26% to a high of 67%. Clearly, Dr. Kyle engineered her placebo to resemble the trend in MMEs. In any analysis, it is possible to replace a theoretically relevant outcome with one that is unrelated but highly correlated and thereby demonstrate a similar model fit with nonsense results. This is hardly the point of placebo tests and given the wide availability of public time series data, it is not surprising that the defendants' experts were able to find such series. These analyses prove nothing.

54. While placebo tests have a place in econometric practice, an important component of causal inference in economics is theory, informed by institutional knowledge. This theoretical and empirical foundation is precisely what I lay out in my affirmative report prior to developing my econometric model. It is not just arbitrary that I include price and promotion as the key explanatory variables in my model of the opioid market. These are the variables that capture the economic levers that in theory increase or decrease sales over time. Promotion is not only theoretically related to sales, but also discussed throughout the defendants' documents as a major determinant of sales. There is an extensive previous literature demonstrating the relationship between promotion and sales. Thus, the causal inferences about impact that I generate in my affirmative report are the combined product of theory, institutional knowledge, and statistical analysis.

C. Defendants Mischaracterize Moderators as Omitted Variables

55. The motion argues that "because she fits her model to the data, her model does not accurately predict real-world events that may have influenced opioid prescribing, like changing medical standards and drug reclassification."[72] The purpose of my model, however, was not to separately estimate the effect of individual market changes that facilitated or counteracted the defendants' detailing efforts but to capture the net effect of these factors combined. Many of the "real-world events" that contributed to prescribing increases listed in the motion – such as the APS and AAPM guidelines – were alleged to have been part of the scheme to increase opioid use. Others were the product of promotion – such as increased prescriptions for post-surgical and trauma pain. As such, they are properly treated as "effect moderators" and thus should not be controlled for in the model. The countervailing public health "events" (and longitudinal efforts such as reporting of opioid deaths) are also properly treated as effect moderators and their effects are captured in gradual decline in the effectiveness of promotion in the

[72] Motion to Exclude, p. 13.

third era. For the purposes of estimating the impact of the alleged unlawful conduct, my estimated models are reliable and as granular as they need to be.

56. In the table below I provide a detailing listing of the specific factors named in this part of the motion. Not all variables have the same impact in the context of my aggregate model. Below I characterize each variable as to whether it should be considered as a moderator that was influenced by defendants' misconduct, or irrelevant.

Table 1. Omitted Variable Characterization

Variable[73]	Variable Characterization	Evidence
Medical Guidelines for Treatment of Pain	Influenced by defendants' Misconduct	As I discuss in this report and in my original report, the emergence of medical guidelines for pain treatment from groups such as the APS, AAPM, and the JCAHO were largely influenced and due to defendants' misconduct.[74]
Increase in Surgery and Trauma-related opioid prescriptions	Irrelevant or Influenced by defendants' Misconduct	The defendants produce no data or literature to suggest this is true.[75] On the contrary, data that I prepared for my original report shows that the incidents of trauma care decreased by 3.5% and the incidents of inpatient- and outpatient-surgeries decreased 9.9% from 1995 to 2018.[76] To the extent that the use of opioids increased for trauma and surgical patients despite the decrease in cases, those effects should not be considered to be independent of marketing.
Patient Preferences and Loyalty	Irrelevant or Influenced by defendants' Misconduct	Patient preferences are typically treated as a variable that differs cross sectionally, not over time. In that case, they would be irrelevant to my model. Any longitudinal changes in patient preferences or "loyalty" that does occur would properly be treated as the product of marketing or the addictive nature of opioids – and it would be inappropriate to remove these effects from my estimates.
Drug Reimbursement Policy	Influenced by defendants' Misconduct	In other sections of my report I explain in further depth how the defendants' exerted great efforts to influence drug reimbursement policies and achieve more advantageous positions on formularies.[77]

[73] Motion to Exclude, p. 18.

[74] See ¶ 10 and footnote 8 of this reply report; Rosenthal Report, ¶ 66.

[75] Motion to Exclude, p. 18.

[76] Rosenthal Report, Table 6, Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) and Health Resources and Services Administration (HRSA) Area Health Resource File (AHRF).

[77] See ¶82 of this reply report.

Number of Military Veterans	Irrelevant	As I state in this report, the number veterans as well as homeless veterans has decreased and is projected to continue to decrease.[78]
Number of Doctors	Irrelevant	While the number of practicing physicians has increased the underlying prevalence of indications for which opioids would be appropriately used for (trauma and surgery) has declined during this period.[79] In such a context, the number of physicians would not be expected to have a meaningful relationship with prescribing.
Number of Hospitals	Irrelevant	The number of hospitals, hospital beds, and occupancy of hospitals has also been decreasing.[80]
Number of Pill Mills	Influenced by defendants' Misconduct	This is an odd variable for defendants to reference since the proliferation of 'pill mills' are due to defendants' negligence and misconduct.[81]

[78] C. Richardson and J. Waldrop, "Veterans: 2000," *US Department of Commerce, Economics and Statistics Administration, US Census Bureau,* 8(2), 2003, pp. 1-11; RAND Health, "Current and Future Demographics of the Veteran Population," *Current and Projected Characteristics and Unique Health Care Needs of the Patient Population Served by the Department of Veterans Affairs,* RAND Corporation, 2015, pp. 31-56, p. 40.

[79] Organisation for Economic Co-Operation and Development, OECD Health Data, July 26, 2019 (https://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_WFMI); See also Rosenthal Report, Table 6, Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) and Health Resources and Services Administration (HRSA) Area Health Resource File (AHRF).

[80] Centers for Disease Control and Prevention, "Hospitals, beds, and occupancy rates, by type of ownership and size of hospital: United States," 2017, Table 89, selected years 1975–2013.

[81] "The Controlled Substances Act requires drug companies to control against diversion, and to design and operate systems to identify 'suspicious orders,' defined as 'orders of unusual size, orders deviating substantially from a normal pattern, and orders of unusual frequency.' The companies are supposed to report such orders to the DEA and refrain from shipping them unless they can determine the drugs are unlikely to be diverted to the black market." And "From 2003 to 2011, Mallinckrodt shipped a total of 53 million orders, flagged 37,817 as suspicious but stopped only 33 orders, the plaintiff's filing states…In a settlement with the DEA, Mallinckrodt agreed that from Jan. 1, 2008, through Jan. 1, 2012, 'certain aspects of Mallinckrodt's system to monitor and detect suspicious orders did not meet the standards' outlined in letters from the DEA deputy administration for diversion control." S. Higham, S. Horwitz, and S. Rich, "Internal drug company emails show indifference to opioid epidemic," The Washington Post, July, 2019 (https://www.washingtonpost.com/investigations/internal-drug-company-emails-show-indifference-to-opioid-epidemic-ship-ship-ship/2019/07/19/003d58f6-a993-11e9-a3a6-ab670962db05_story.html?noredirect=on&utm_term=.0a8654b0985f).

D. The Motion to Exclude Relies on Incorrect Tests for Unit Roots

57. In Section D.2, the motion introduces the issue of unit roots and incorrectly claims that (a) I did not even test my model for stationarity – which I did, and (b) I incorrectly asserted that my model does not suffer from this issue – which it does not.[82,83]

58. The motion is in error on both points. The motion to misrepresents my testimony.[84] And the motion inappropriately relies on the defendant's incorrect expert reports of Dr. Cantor and Dr. Kyle to support their assertions about unit roots.[85] While both Dr. Cantor and Dr. Kyle claim that my dependent variable is non-stationary, they differ in how they test for unit roots. And nevertheless, both are wrong.

1) Unit Roots and Trend Stationarity

59. Dr. Kyle failed to check to see my dependent variable was trend stationary. By failing to de-trend, a time-series unit root test like Dickey-Fuller can falsely report there is a unit root when there is none.[86] When a data series increases along a trend, like population, one needs to account for the possibility of a trend by detrending the series before testing for unit roots. This is one of the most basic assumptions to impose when conducting unit root tests in time-series analysis because so many time-series variables follow a trend. This is a basic mistake that Dr. Kyle made, and Dr. Cantor did not. Dr. Kyle could have avoided this mistake by implementing the testing options that included a constant and a trend as opposed to stopping with the first one that indicated that unit roots existed.[87]

60. In seeking sources to cite in support of this point, I do not need to proceed any further than Exhibit 12 to the motion.[88] Hill and Griffiths point to Figure 12.2(c) as an example of a 'de-trended' series that "has a constant variance and covariances that depend only on time separating observations,

[82] Motion to Exclude, pp. 16-18.

[83] Deposition of Meredith Rosenthal, Ph.D., in this matter, May 4, 2019, 139:13-15.

[84] I made clear in my deposition that my staff had tested for unit roots and found none, *Ibid.*, 137:13-17. I could not recall at that time whether the underlying series were stationary (vs. trend stationary), but I was certain that we rejected the possibility of spurious findings caused by unit roots and communicated that conclusion.

[85] Expert Report of Robin Cantor, Ph.D., in this matter, May 10, 2019 (hereafter, "Cantor Report"); Expert Report of Margaret Kyle, Ph.D., in this matter, May 10, 2019 (hereafter, "Kyle Report"), ¶ 116.

[86] Exhibit to Motion to Exclude, Exhibit 12, R. Hill, W. Griffiths, and G. Lim, "Regression with Time-Series Data: Nonstationary Variables," *Principles of Econometrics*, John Wiley & Sons, Inc., 2011, pp. 474-497, p. 485.

[87] *Ibid.*

[88] *Ibid.*

not the time at which they are observed. In other words, the 'de-trended' series is stationary."[89] Dr. Cantor, on the other hand, did recognize the necessity to de-trend a series prior to testing for unit roots so she can proceed to the next unit root issue.

2) Unit Roots and Structural Breaks

61. The second fundamental concept in the analysis of unit roots that Dr. Cantor recognizes (but Dr. Kyle again does not) is the importance of structural breaks when testing for unit roots. To address this issue, one must advance past introductory econometrics texts and be familiar with more advanced econometric literature. The seminal article on this point shows "how standard tests of the unit root hypothesis against trend stationary alternatives cannot reject the unit root hypothesis if the true data generating mechanism is that of stationary fluctuations around a trend functions which contains a one-time break."[90] In short, if there is a break in a trend, and that break is ignored, then a standard unit root test will conclude that there is a unit root when in fact there is none. "Trend breaks appear to be prevalent in macroeconomic time series, and unit root tests therefore need to make allowance for these if they are to avoid the serious effects that unmodelled trend breaks have on power."[91]

62. There is a clear and obvious structural break in the sale of opioid MMEs around 2012. Ignoring this structural break will tilt unit root tests, like the Dickey-Fuller, towards falsely finding the presence of unit roots when there are none. Dr. Cantor makes an effort to account for a structural break in her unit root test, but her effort falls short of providing a helpful criticism of my model.

63. There are multiple ways to test for unit roots in the presence of structural breaks. One way is to apply unit root tests that are constructed to account for structural breaks. Generally, the approach to testing in the presence of structural breaks is to again de-trend the series but allowing the trend to change at the point of the structural break. There are tests when there is one and only one structural break with a known time for of the break,[92] there are tests when the point of structural break is

[89] *Ibid,* pp. 479-480.

[90] P. Perron, "The great crash, the oil price shock, and the unit root hypothesis," *Econometrica: Journal of the Econometric Society*, 57(6), 1989, pp. 1361-1401, p. 1361.

[91] D. Harvey, S. Leybourne, and A. Taylor, "Testing for unit roots in the possible presence of multiple trend breaks using minimum Dickey-Fuller statistics," *Journal of Econometrics*, 177(2), 2013, pp 265-284, p. 265.

[92] E. Zivot and D. Andrews, "Further evidence on the great crash, the oil-price shock, and the unit-root hypothesis." *Journal of Business & Economic Statistics,* 10(3), 1992, pp. 251-270.

unknown, there are tests when there are multiple structural breaks with known break points[93] and unknown break points,[94] and unknown number of smooth breaks.[95]

64. The approach that Dr. Cantor took to structural break was to account for the break at October 2011 and tested for unit roots before and after that point.[96] Dr. Cantor's approach is not dissimilar to the approach I took prior to beginning my analysis.

65. My staff examined whether the data series used in the regression model were characterized by unit roots before I specified and estimated the model. The problem of spurious regression arises if both the dependent variable and one or more of the independent variables share a common stochastic trend; only if both have unit roots could an independent variable appear to have a causal effect on the dependent variable that reflects a shared common trend only (i.e., one that is actually spurious).[97]

66. Table 2 shows robustness checks using alternative dates for the breakpoints (in particular, the dates of the first and second breaks are shifted forward and backwards by three months)[98]. Results consistently show statistically significant breaks in the "mme_eutrx" series, and consistently reject unit roots in the detrended series. While these tests were run before I specified and estimated the regression model presented in my affirmative report, I have also checked whether unit roots would be similarly rejected if I used the breakpoints determined via estimation of the report's regression model (March 2002 and August 2010). The result (shown in the bottom line of the table) is qualitatively the same as was derived in the pre-tests: the Augmented Dickey-Fuller (ADF) test does not show the detrended series to have a unit root.

[93] R. Lumsdaine and D. Papell, "Multiple trend breaks and the unit-root hypothesis," *Review of Economics and Statistics,* 79(2), 1997, pp. 212-218.

[94] P. Narayan and S. Popp, "A new unit root test with two structural breaks in level and slope at unknown time," *Journal of Applied Statistics* 37(9), 2010, pp. 1425-1438.

[95] R. Becker, W. Enders, and J. Lee, "A stationarity test in the presence of an unknown number of smooth breaks," *Journal of Time Series Analysis,* 27(3), 2006, pp. 381-409.

[96] Cantor Report, Backup materials: 03 - Spurious Regressions ADF and KPSS Unit root Tests.sas

[97] J. Wooldridge, "Advanced Time Series Topics," *Introductory Econometrics: A Modern Approach*, South-Western Cengage Learning, 2013, pp.632-675, pp. 644-646.

[98] A more detailed explanation of the approach and a representative set of results is shown in Appendix B.

Table 2. Unit Root Structural Break Robustness Tests

Robustness tests								
	1st break date	2nd break date	All marginal coefficients on splines statistically significant?	Augmented Dickey Fuller (ADF) test statistic	Critical values for the ADF test statistic			Inference from test statistic*
					1%	5%	10%	
Main pretest specification	2001m1	2011m7	Yes	-14.647	-3.456	-2.878	-2.570	
Alternatives in pretest								
1st break date back 3 months	1999m10	2011m7	Yes	-14.762	-3.456	-2.878	-2.570	No unit root
1st break date forward 3 months	2001m4	2011m7	Yes	-14.461	-3.456	-2.878	-2.570	No unit root
2nd break date back 3 months	2001m1	2011m4	Yes	-13.149	-3.456	-2.878	-2.570	No unit root
2nd break date forward 3 months	2001m1	2011m10	Yes	-15.179	-3.456	-2.878	-2.570	No unit root
Using break dates from promotion model								
Model break dates	2002m3	2010m8	Yes	-8.860	-3.456	-2.878	-2.570	No unit root

* The fact that the ADF test statistic exceeds the 1% critical value (in absolute value) implies the null hypothesis of non-stationarity can be rejected, i.e. the mme_eutrs series does not contain a unit root.

E. Endogeneity

67. The motion asserts that my model suffers from endogeneity bias. I disagree.

68. I note that there is no statistical basis for the defendant's endogeneity charge set forth in either the motion or the defendants' expert reports. All of the discussion they provide regarding endogeneity is general and theoretical, with no empirical evidence.

69. Endogeneity is a broad econometric issue that can encompass many different circumstances. The motion gives cursory treatment of this issue and provides only one intuitive example, which is not applicable to my national, aggregate model.[99] Furthermore, their citations to my deposition testimony are incomplete and taken out of context.[100]

[99] Motion to Exclude, p. 17.

[100] The Motion to Exclude cites my deposition at 330:25-331:13 and 336:16-337:21. My deposition testimony at

70. The motion's assertion that my national, aggregate, time-series model suffers from a biased estimate of the effectiveness of promotion is not correct. While many of the defendants' experts raised this issue, they did not appropriately consider the context and none of them provided empirical evidence that demonstrates the existence of endogeneity, much less report the magnitude of bias. The collective concern was limited to the "potential" for endogeneity.

71. The defendants' experts make many references to academic studies where endogeneity was a legitimate issue. Just because promotion was treated as endogenous in some studies, however, does not mean that promotion must be treated as an endogenous variable in my national, aggregate, time-series model. For example, a typical and straightforward assumption is that promotion causes sales. At the most abstract level, the concept of endogeneity arises when changes in sales (i.e., dependent variable) have an influence on promotion (i.e., an explanatory variable). This type of relationship is referred to as "reverse causality" or a "feedback cycle".[101] While this phenomenon may be real, as a statistical issue the choice of time period to measure sales and promotion is an important factor when considering the potential econometric properties of endogeneity.

72. My aggregate model is constructed to explain aggregate monthly pharmaceutical opioid sales (the dependent variable) as a function of aggregate monthly count of detailing visits (the explanatory variable) while allowing for time-varying (net) effectiveness of promotion. In my models, I chose to measure sales as MME (morphine milligram equivalents), which can be observed by manufacturers over the course of a specified unit of time such as week, month or year. Actual sales (after returns) can be observed by the manufacturer with a lag. From a data analyst perspective, monthly sales data are available.

73. As an econometric issue, the concern with endogeneity must be stated precisely: the changes in the dependent variable must *be contemporaneous* with the changes in the explanatory variable. That is, feedback or reverse causality effect must take place within the same unit of time as the effect of the

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this point is merely providing an innocuous and benign definition of endogeneity. There are multiple, incorrect efforts by the defense attorney to equate the endogeneity issues that arise in physician-level data and analysis, which I acknowledge, to the endogeneity in an aggregate model, which I maintain does not occur in my analysis. Moreover, none of the defendants' economic experts provided any empirical tests or demonstrations that endogeneity does exist; all that is offered is conjecture and speculation.

[101] Kyle Report, ¶121; Expert Report of Pradeep Chintagunta, Ph.D., in this matter, May 10, 2019 (hereafter, "Chintagunta Report") ¶77; Expert Report of Iain Cockburn, Ph.D., in this matter, May 10, 2019 (hereafter, "Cockburn Report"), ¶73 and ¶78; Expert Report of Jonathan Ketcham, Ph.D., in this matter, May 10, 2019 (hereafter, "Ketcham Report"), Section XI.F.2.

explanatory variable on the dependent variable. The potential for endogeneity will depend on the unit of time of analysis.

74. The motion provides the support for this issue in their Exhibit 13.[102]

> "If the regressors are contemporaneously uncorrelated with the disturbance vector, the OLS estimator is biased but retains its desirable asymptotic properties. Contemporaneous uncorrelation in this context means that the nth observation on all regressors must be uncorrelated with the nth disturbance term, but it is allowed to be correlated with the disturbance terms associated with other observations. … OLS will be biased, but consistent. In this case no alternative estimators are available with superior small-sample properties, so the OLS estimator is retained on the basis of its desirable asymptotic properties. Henceforth the 'contemporaneous' qualification is dropped for expositional ease, so that the terminology 'regressor correlated with the error' mean contemporaneous correlation."[103]

75. Indeed, the motion ignores this important qualification and its implications. To restate, the motion, to be consistent with the explanation given by a standard textbook, would have to say "Endogeneity occurs where there is a [*contemporaneous*] correlation between the explanatory variable and the error term."[104]

76. The motion continues to say that "detailing (the explanatory variable) and opioid sales (the dependent variable) are simultaneously determined"[105] without carefully evaluating the implications of that statement. The specific example put forward by the motion may be relevant when empirical analysis is being conducted on behalf of a single firm evaluating its promotional effectiveness for a single drug. An example of a firm targeting high prescribers is readily available in this case. Purdue specifically targets the physicians in the highest two deciles for both primary care physicians and specialists.[106] An analysis that uses the variation in promotion at the physician level to identify its impact would indeed need to consider such targeting as a source of endogeneity.

77. My analysis, however, is at the national, aggregate level. The detailing variable is summed across multiple manufacturers (both defendants and nondefendants) across multiple drugs (sold by

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[102] Exhibit to Motion to Exclude, Exhibit 13, P. Kennedy," Violating Assumption Four: Instrumental Variable Estimation," *A Guide to Econometrics*, Blackwell Publishing, 2008, pp. 137-141.

[103] *Ibid.*, pp. 137-138.

[104] Motion to Exclude, p.17.

[105] *Ibid.*

[106] "Two biggest promotional drivers for the OxyContin brand: OxyContin Primary presentations to high decile HCPs have an ROI of 3.7" PPLP003449398-435, at 402. See also: PPLP003420990-1051 at 1044; PPLPC025000148523 at slides 8 and 9.

defendants and nondefendants) including some that have zero marketing efforts in a given period, and across physicians. Similarly, opioid sales (the dependent variable) is computed as the sum of all MME sales across all manufacturers (defendants and nondefendants) across all drugs (brand drugs, generic drugs, and authorized generic drugs).

78. For the assertion in the motion—that detailing and sales to be simultaneously determined—to be true, it would have to be demonstrated at this aggregate level, and aggregate sales in a month would have to be able to determine aggregate detailing in that same month. No defendant expert conducted such an analysis. Nor is there any conceptual basis for the motion to assert that aggregate detailing is simultaneously determined with aggregate sales given that there are so many different decision makers and sources of detailing and sales information.

V. Defendants' Criticism of My Indirect Model Lacks an Empirical Basis

79. The motion suggests that the exclusion of specific variables that could account for opioid use in a track one county might bias the estimate of impact I obtain from my "indirect" model.[107] These statements (and the expert opinions they are based on) confuse the nature of the analysis, which extrapolates a cross-sectional model of county-level use based on the trends observed in a set of explanatory variables. For any omitted variable to have an effect on my estimate of excess opioid MMEs due to the misconduct, it would have to change over time and be a significant predictor of MMEs at the county level, controlling for all the variables already included in the model. In fact, several of the factors listed in the motion to where the posited relationship to opioid sales should be positive actually *decrease* over time.[108] Moreover, in no instance does the motion demonstrate that inclusion of an independent (that is, unaffected by the defendants' conduct) factor would alter my estimate of impact. The defendants' experts have not produced such an analysis. As such, these "omitted variables" arguments are unsubstantiated.

80. Notably, (as summarized above in Table 1) the defendants' list of "omitted" variables also includes phenomena that are alleged to have been directly affected by the misconduct. It is important to understand that when the defendants argue that my estimate of impact is "biased" by the fact that I do not *eliminate* the influence of factors such as the APS/AAPM guidelines, they are also admitting that my

[107] Motion to Exclude, pp. 17-18.

[108] For example, the absolute number and proportion of veterans has been decreasing from 1980, see: C. Richardson and J. Waldrop, *opt. cit.*; RAND Health, *opt. cit.* The number of hospitals, hospital beds, and occupancy of hospitals has also been decreasing, see: Centers for Disease Control and Prevention, 2017, *op. cit*.

estimate does capture these effects – as I intended. These factors include: medical guidelines, patient preference, loyalty to certain classes of drugs, and drug reimbursement policy.[109] It is clear from the complaints that the plaintiffs intend to prove that medical guidelines were used as a tool by the defendants to open the floodgates of prescribing; any notion that my analysis should "control" for the issuance of such guidelines is non-sensical.[110]

81. Patient preferences and loyalty to specific drugs and classes are also not independent of the allegedly unlawful marketing – indeed, shaping preferences is a key objective of marketing. No economist would consider these to be independent factors in an analysis of the effect of marketing on sales – no published analysis in pharmaceutical economics that I have seen does so.

82. In the case of drug formularies and coverage policies there is ample discovery material that speaks to the targeting of health insurers and pharmacy benefit managers by manufacturers. Purdue had an "OxyContin Formulary Kit" intended to be sent to members of Pharmacy and Therapeutics (P&T) committees,[111] which petitioned the committee members to give OxyContin favorable formulary status.[112] This mailing includes a "Formulary Package," which is an 85-page monograph on OxyContin that conveys four of the defendants' marketing messages that are challenged in this lawsuit: (1) It promotes the use of OxyContin for chronic, non-Cancer pain;[113] (2) it distinguishes physical dependence from addiction, and it downplays the importance of dependence;[114] (3) it propagates the notion of *pseudo-addiction* (without directly using that term);[115] and (4) it understates the likelihood of addiction

[109] See Table 1 in this report.

[110] It is alleged by the plaintiffs, and evidence has been produced in this case that the promotional efforts of the American Pain Society (APS), American Academy of Pain Medicine (AAPM), Federation of State Medical Boards (FSMB), Joint Commission on Accreditation of Healthcare Organizations (JCAHO), and other organizations were funded in part by the defendants. See: Government Accountability Office, "OxyContin Abuse and Diversion and Efforts to Address the Problem," GAO-04-110, 2003, pp.22-24; PPLP003477086-125 at 109-112; PDD9273201211-288 at 224; ENDO-OPIOID_MDL-02298417; and JAN-MS-00494171 at slide 35. To the degree that guideline-disseminating organizations like APS, JCAHO and others disseminated fraudulent messages, measures of the promotion effects of these groups cannot be used as controls for other factors that contributed to opioid sales growth.

[111] PKY180114038-145.

[112] *Ibid.,* at 039.

[113] *Ibid*., at 097-102.

[114] *Ibid*., at 111.

[115] *Ibid*., at 121. It states, "Tolerance and physical dependence in pain patients are not signs of psychologic dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control."

to OxyContin.[116] Purdue also employed people called Medical Liaisons, who marketed its drugs to decision makers at managed care organizations and hospitals.[117] Endo had employees called "HOPE Field Scientists," whose role was to persuade P&T committee members to place Opana ER on the formulary.[118] Janssen had a plan for promoting Nucynta ER in 2012, outlined in a presentation, "Market Access Priorities 2012."[119] One prong of that plan was "Increasing Awareness/Demand," which involved direct promotion to health plans: "Awareness: Series of e-Blasts/ Direct Mail to Payers: E-mail/mail directly to medical and pharmacy directors."[120] Thus, to argue that changes in formularies or coverage are an independent cause of sales rather than the effect of Defendant manufacturers' scheme is clearly untenable.

VI. Defendants' Criticisms of My Appropriate Use Analysis are Unfounded

83. In the motion, the defendants rely upon purely legal arguments to attempt to dismiss the implications of my analysis regarding whether the ostensible growth in appropriate use of opioids might explain the rapid growth observed in MMEs between 1995 and 2018. Specifically, the defendants argue: "Rosenthal's 'thought experiment' is improper because it depends on other experts' flawed and unsupported medical assumptions of which opioid uses are medically appropriate… And Rosenthal's reliance on Dr. Schumacher is improper as this Court and others have repeatedly confirmed that '[a] scientist, however well credentialed [s]he may be, is not permitted to be the mouthpiece of a scientist in a different specialty.'"[121]

84. In my experience, it is common for an expert to rely on the conclusions of other experts (i.e., to assume that the fact finder accepts the conclusions of another expert, with those opinions then becoming a springboard for the opinion of another expert). In this case, I am not acting as "the

[116] *Ibid*., at 121. It states, "Iatrogenic 'addiction' to opioids legitimately used in the management of pain is very rare."

[117] PDD9520815001-118, at 014

[118] As noted below, Endo's HOPE program (Health Outcomes and PharmacoEconomics) promoted the benefits of Endo's drugs to managed care organizations. The HOPE program was responsible for two articles published in managed care journals (T. Berner et al., "A Comparison of Daily Average Consumption of Oxycodone Controlled Release (OxyContin CR) and Oxymorphone Extended Release (Opana ER) in Patients with Low Back Pain," *Pharmacy and Therapeutics*, 36(3), 2011, 139-144; M. Rubino et al., "A comparison of daily average consumption (DACON) of oxycodone and oxymorphone long-acting oral tablets," *Journal of Managed Care Pharmacy*, 17(5), 2011, pp. 367-376).

[119] JAN-MS-00010968-985.

[120] *Ibid*., at 982-983.

[121] Motion to Exclude, pp. 13-14.

mouthpiece" for Schumacher; I am merely applying Schumacher's conclusions to validate an input to my analysis. In so doing, I am not vouching for the correctness of Schumacher's conclusions.

85. The defendants also argue: "Rosenthal also makes her own medical assessments…. For example, to calculate the appropriate opioid dosage for patients suffering from surgical and trauma pain, Rosenthal selects 30 MMEs over seven days based on MD Anderson Cancer Center's Postoperative Pain Management Guidelines."[122] On the contrary, I am not making my own medical assessment here. Rather, I use inputs from a standard set of published medical guidelines; given a range of 20-40 MMEs, I reasonably selected the center of the range. This is appropriate for a thought experiment intended to reach an approximate estimate. Moreover, I use a standard sensitivity analysis to show how my results would change if any of these inputs were increased. I am by no means making medical judgments in this section. Rather I am determining whether changes in incidence of the conditions that clinical experts have opined are appropriately treated by opioids are of a magnitude that could possibly explain the increases in opioid use in the decades after 1995. It is clear that they cannot.

86. The defendants further argue: "Once stripped of the medical judgments that she is not qualified to make, Rosenthal's 'thought experiment' does nothing more than apply arithmetic... But an 'expert is precluded from offering testimony that is not based on any specialized knowledge, but rather involves 'basic calculations.'"[123] Both the framing and execution of my analysis require expertise and specialized knowledge – including the expertise to select the appropriate data sources, categories of utilization, and identify all the relevant inputs. Moreover, it is not proper to consider this analysis on its own. This is not my sole or primary analysis; it is an estimate used to reject an alternative explanation of the results of my primary analysis. Through this thought experiment, I show that the alternative explanation does not come close to explaining the high level of opioid prescriptions. This approach to triangulating the main results of my affirmative report is a standard technique in social science.[124]

[122] Motion to Exclude, p. 15.

[123] *Ibid.*

[124] S. Olsen, "Analysis Through Tri-angulation and Synthesis to Interpret Data in a Mixed Methods Evaluation," from *Evaluation Design for Complex Global Initiatives: Workshop Summary,* Washington, DC: the National Academies Press, 2014, (https://www.nap.edu/read/18739/chapter/9); Open University, "PUB 695 3.0, Triangulation," June 28, 2018 (http://www.open.edu/openlearncreate/mod/page/view.php?id=65924).

VII. Summary and Conclusion

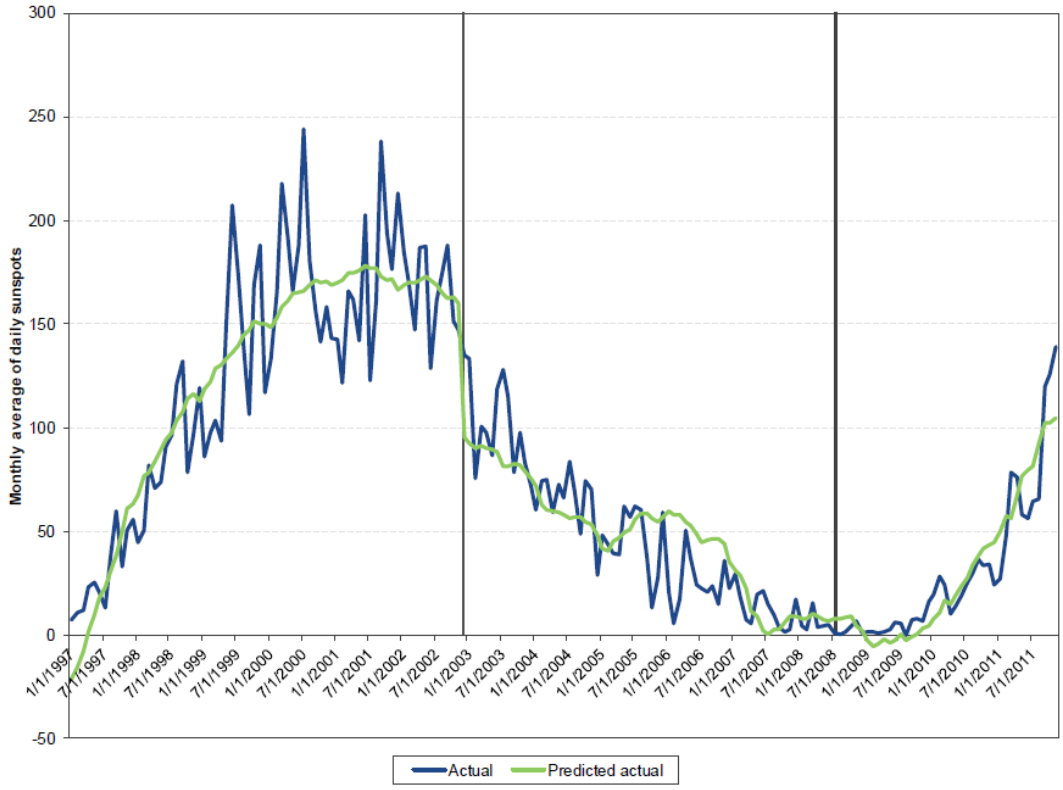
87. In summary, the defendants' attempts to invalidate my opinions fail. Perhaps not surprisingly, they appear to ignore a key element of the opioid epidemic that animates my results: the spiral of tolerance and addiction that leads patients to higher and higher doses. They also try to cast the hallmarks of the scheme – the desensitization of physicians, patients, payers, and regulators to the risks of opioid addiction – as "independent" influences whose effects should be parsed from my estimates. The methodological flaws in my analysis that the defendants claim to show, including the failure to correct for endogeneity and unit roots, are non-existent.

Appendix A: Placebo Tests

1. The motion mischaracterizes my selection of turning points for my analysis. I have addressed this criticism in detail in Section III of my report. In this appendix, I respond to Dr. Kyle who blindly implements a grid search to identify turning points that would somehow align detailing contacts with changes in average monthly sunspots.

2. Dr. Kyle states, "For this analysis, I use data from NASA on the monthly average of daily sunspots from January 1997 through November 2011."[1] She does not offer an explanation or justification for her selection of these months for her analysis. Dr. Kyle's selection of this window of time is a quintessential example of cherry-picking. The result of her analysis is shown in her Figure 37.

Figure 37: Actual vs. predicted monthly average of daily sunspots



Source: Rosenthal backup data; NASA sunspot data. *** indicates 1%; ** indicates 5% significance; * indicates 10% significance.

[1] Kyle Report, ¶ 135.

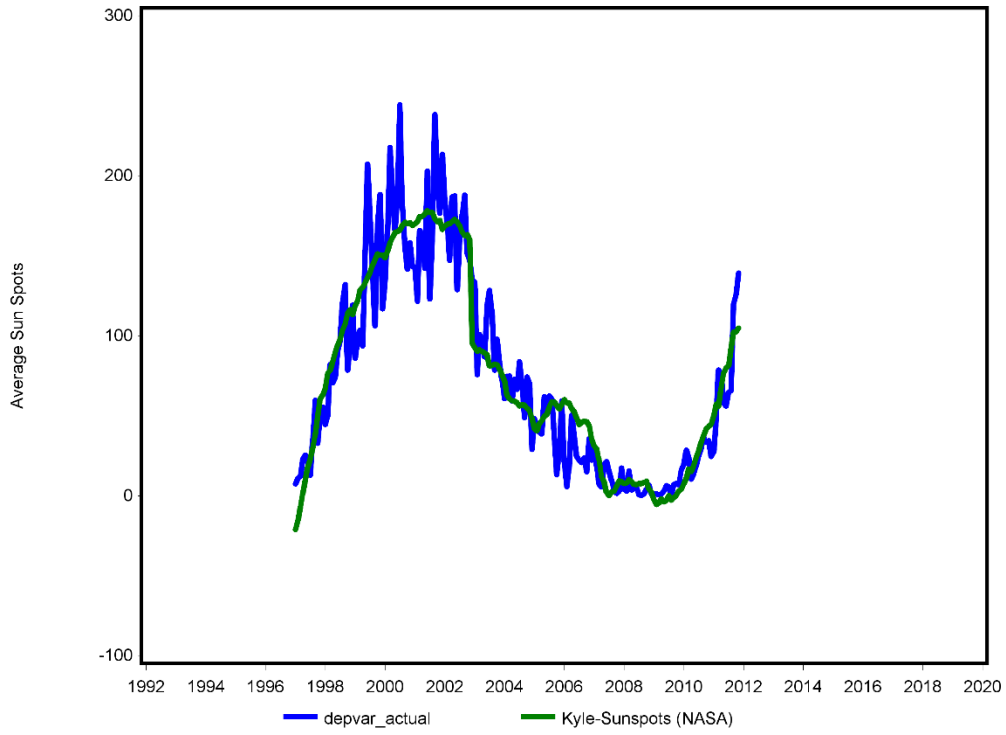
3. I have reproduced her regression analysis in Table A.1 and her below as Figure A.1, except I have changed the horizontal axis to run from January 1993 to May 2018 to be consistent with every other figure in my report.

Table A.1 Reproduction of Kyle's Sunspot Analysis with Cherry-Picked Dates

Nonlinear OLS Summary of Residual Errors								
Equation	**DF Model**	**DF Error**	**SSE**	**MSE**	**Root MSE**	**R-Square**	**Adj R-Sq**	**Label**
avg_sunspots	6	173	87960.5	508.4	22.5487	0.8787	0.8752	Kyle-Sunspots (NASA)

Nonlinear OLS Parameter Estimates					
Parameter	**Estimate**	**Approx Std Err**	**t Value**	**Approx Pr > |t|**	**Label**
a	153.8231	34.5115	4.46	<.0001	Constant
b1	0.000333	0.000041	8.15	<.0001	Stock of Promotion*Regime Dummy Until DEC2002
b2	0.00024	0.000037	6.41	<.0001	Stock of Promotion*Dummy from JUL2008
b3	2.175E-6	4.791E-7	4.54	<.0001	Stock of Promotion*Dummy Trend from JUL2008
x	0.064792	0.00768	8.43	<.0001	Depreciation Rate Constant
main0	-171.702	26.0949	-6.58	<.0001	Fisher Ideal Price Index

Figure A.1 Reproduction of Kyle's Sunspot Analysis with Cherry-Picked Dates



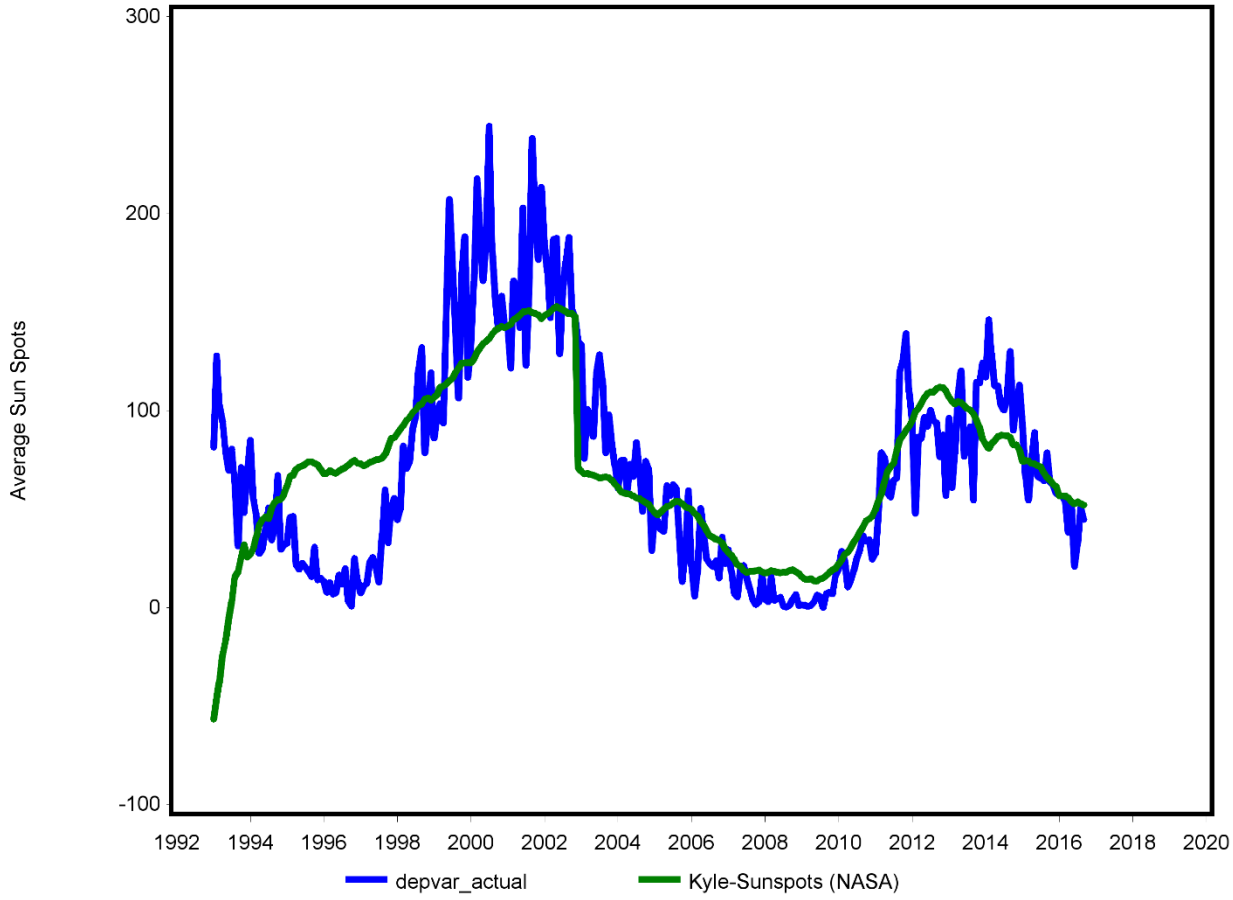
4. For my direct analysis I rely on IQVIA data beginning in January 1993 and ending in May 2018 for a total of 305 months of observations. However, the NASA sunspot data that Dr. Kyle uses ends at September 2016, thus only 284 months of data are available for analysis starting from January 1993. To demonstrate the advantages of Dr. Kyle's cherry-picking efforts, I use the NASA sunspots data starting in January 1993 through September 2016 (when the NASA data ends). With this data I rerun my model B and obtain the results shown below in Table A.2 and Figure A.2. By including the months of data that Dr. Kyle inexplicably excluded, her adjusted R-squared drops from her reported 88% to 55%.

Table A.2 Dr. Kyle's Analysis Using All Available NASA Sunspot Data

Nonlinear OLS Summary of Residual Errors								
Equation	**DF Model**	**DF Error**	**SSE**	**MSE**	**Root MSE**	**R-Square**	**Adj R-Sq**	**Label**
avg_sunspots	6	279	381126	1366.0	36.9600	0.5607	0.5528	Kyle-Sunspots (NASA)

Nonlinear OLS Parameter Estimates					
Parameter	**Estimate**	**Approx Std Err**	**t Value**	**Approx Pr > |t|**	**Label**
a	-35.2803	35.1752	-1.00	0.3167	Constant
b1	0.000219	0.000031	7.13	<.0001	Stock of Promotion*Regime Dummy Until DEC2002
b2	0.000144	0.000024	6.02	<.0001	Stock of Promotion*Dummy from JUL2008
b3	7.492E-7	2.843E-7	2.64	0.0089	Stock of Promotion*Dummy Trend from JUL2008
x	0.041096	0.00551	7.46	<.0001	Depreciation Rate Constant
main0	-31.905	26.8406	-1.19	0.2356	Fisher Ideal Price Index

Figure A.2 Kyle's Analysis Using All Available NASA Sunspot Data



5. Next, I want to take Dr. Kyle's sunspot analysis a step further. NASA provides data on average number of sunspots per month dating back to 1749.[2] Since there is no causal relationship between detail contacts for opioids and the incidents of sun spots in the same month, the experiment proposed by Dr. Kyle could be conducted on any period of 305 months of sunspot data. This would provide a test of the assertion made in the motion that:

> "[I]f one were to replace MME sales in [Rosenthal's] model with data from NASA concerning the monthly average of daily sunspots [], one applying her model would find a causal relationship between physician detailing on the one hand and sunspots [] on the other."[3]

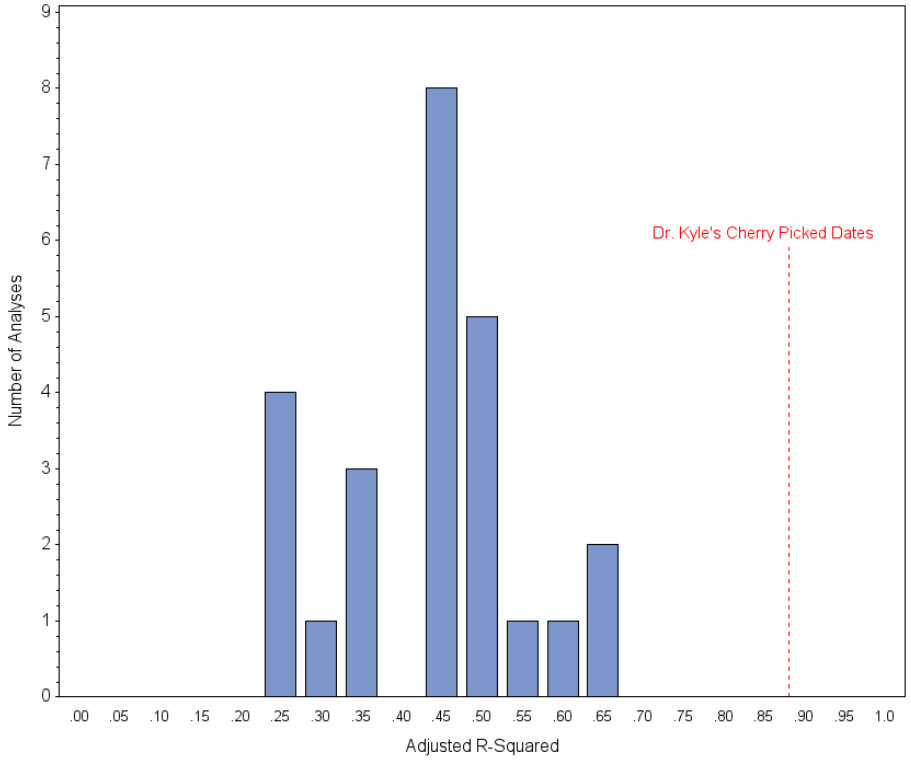
[2] National Aeronautics and Space Administration, "The Sunspot Cycle", Updated 2017/03/15 (https://solarscience.msfc.nasa.gov/SunspotCycle.shtml)

[3] Motion to Exclude, pp. 12-13, citing Ex. 9, Kyle Dep. at 151:3–21; Ex. 10, Kyle Report at ¶ 135.

6. I select 25 sets of 305 months of sunspot data that begin at random points in time between January 1794 and April 1991.4 In each case I apply the same methodology and search criteria, Dr. Kyle used to mechanically select turning points.5 I then ran my Model B with turning points selected for each of the 25 periods of sunspots. The adjusted R-squareds range from a minimum of .26 to a maximum of .67. The distribution has a mean of .44 and a standard deviation of .117. None of the 25 randomly selected windows come close to the 88% reported by Dr. Kyle.

7. To see where Dr. Kyle's cherry-picked result lands within this sample of 25 random starting points see Figure A.3. Assuming the R-squareds are normally distributed, then Dr. Kyle's reported 88% falls over 3 standard deviations outside the mean, statistically different from the mean of .44 with 99.9% confidence. Dr. Kyle's result, which the motion relies on, is clearly a cherry-picked result.

Figure A.3 Distribution of R-Squared from 25 Random Sunspot Analyses, and Dr. Kyle's R-Squared



[4] Given that the NASA data end in September 2016, April 1991 is the latest date that would allow for a full set of 305 months of sunspot data.

[5] Including the date ranges over which Dr. Kyle conducted her search for turning points.

Appendix B: Unit Roots

1. In testing "mme_eutrx" for unit roots, it is clear that account needs to be taken of the multiple breaks in the series; as discussed in my affirmative report,[1] growth in "mme_eutrx" accelerated around 2000, rose to a peak, and declined around 2011. Standard unit root tests are known to be biased towards non-rejection of unit roots in the presence of structural breaks,[2] so mechanical testing for unit roots without taking breaks into account when they are present can be expected to show non-rejection.

2. To allow for the multiple breaks in the data, I first estimated piecewise linear regressions of the following form:

$$Y_t = a + \beta_1 D_1 T_t + \beta_2 D_2 (T_t - T1) + \beta_3 D_3 (T_t - T3) + e_t \qquad (1)$$

Where Yt = mme_eutrx in month t

Tt = number of months since January 1993 in month t

D1=1 from the outset of the data period to a first breakpoint month T1; 0 otherwise

D2=1 starting at month T1+1 and extending through the second breakpoint month T2; 0 otherwise

D3=1 starting at month T2+1 and extending through the end of the data series; 0 otherwise

3. Residuals from this regression can be used to determine whether the "mme_eutrx" trends stochastically (i.e., has a unit root) after the multiple breaks are taken into account. My staff ran model (1) using a number of alternative assumptions about the timing of break points T1 and T2 and ran an alternative version of the model with four rather than two break points. Estimation of (1) always indicated significant breaks in the series, and unit root tests applied to the detrended series always rejected unit roots.

4. To illustrate, the following regression results show results of the baseline specification which hypothesized a first break in January 2000 and a second in July 2011. Results show significant changes in the trend in mme_eutrx at these breakpoints:

[1] Rosenthal Report, ¶¶ 49-57

[2] Perron, *op. cit*.

Table B.1 De-Trending Regression

Number of Observations	305
F(1,301)	19822.0
Prob > F	<.0001
R-Square	0.9924
Root MSE	5.3398E8
Denominator DF	304

Estimated Regression Coefficients				
Parameter	Estimate	Standard Error	t Value	Pr > |t|
Intercept	624,864,116	51,218,022.7	12.20	<.0001
D1	34,902,204	1,120,132.4	31.16	<.0001
D2	76,343,763	1,810,472.6	42.17	<.0001
D3	-190,218,253	3,275,067.1	-58.08	<.0001

Applying the standard Augmented Dickey Fuller test to the detrended series, non-stationarity is clearly rejected at a 1% level of statistical significance: 26%

Table B.2 Dickey-Fuller Unit Root Test after De-Trending Including Trend Breaks

Dickey-Fuller Test for Unit Root — Number of Observations = 304

		--Interpolated Dickey-Fuller--		
	Test Statistic	1% Critical Value	5% Critical Value	10% Critical Value
Z(t)	-14.647	-3.456	-2.878	-2.570

MacKinnon approximate p-value for Z(t) = 0.0000

That is, standard unit root tests do not show this series to have a unit root after the structural breaks in the series are taken into account.[3]

[3] Use of the alternative unit root tests available in Stata, including DF-GLS, Phillips Perron, and KPSS, does not alter this result.

Attachment A

Materials Relied Upon

Expert Reports

Expert Report of Henry Grabowski, Ph.D., in this matter, May 10, 2019.

Expert Report of Iain Cockburn, Ph.D., in this matter, May 10, 2019.

Expert Report of Jonathan Ketcham, Ph.D., in this matter, May 10, 2019.

Expert Report of Margaret Kyle, Ph.D., in this matter, May 10, 2019.

Expert Report of Mark A. Schumacher, M.D., Ph.D., in this matter, March 25, 2019.

Expert Report of Meredith Rosenthal, Ph.D., in this matter, May 10, 2019.

Expert Report of Pradeep Chintagunta, Ph.D., in this matter, May 10, 2019.

Expert Report of Robin Cantor, Ph.D., in this matter, May 10, 2019.

Other Legal Documents

Declaration of Timothy W. Knapp in Support of Defendants' Motion to Exclude Meredith Rosenthal's Opinions and Proposed Testimony, June 28, 2019.

Deposition of Meredith Rosenthal, Ph.D., in this matter, May 4, 2019, 139:13-15.

Expert Report of Meredith Rosenthal, Ph.D., in the matter of Neurontin MDL (Kaiser), August 11, 2008, (https://www.communitycatalyst.org/pal-docs/neurontin_exh_F.pdf)

In Re Neurontin Marketing and Sales Practices Litigation, MDL NO. 1629. Civil Action No. 04-cv-10981-PBS.

Memorandum in Support of Defendants' Motion to Exclude Meredith Rosenthal's Opinions and Proposed Testimony, in this matter, June 28, 2019.

Second Amended Complaint Demand for Jury Trial, *In Re National Prescription Opiate Litigation*, United States District Court, For the Northern District of Ohio, Eastern Division, 17-MD-2804.

Bates-Numbered Documents

ACTAVIS0006823-830

ENDO-CHI_LIT-00214471

ENDO-OPIOID_MDL-02298417

JAN-MS-00010968-985

JAN-MS-00494171

PDD9273201211-288

PDD9520815001-118

PKY180114038-145.

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PPLP003420990-1051

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Centers for Disease Control and Prevention (CDC), morphine milligram equivalents conversion.

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IQVIA (formerly IMS Health), Integrated Promotional Services data (IPS).

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